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Master in Bioinformatics (BIS)

In silico analysis of Continuous glucose monitoring (CGM) results in diabetes mellitus patients; and Automatic Event Detection Using Neural Networks

A thesis submitted as a fulfilment of requirements for a Master's degree in Bioinformatics

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Table of Abbreviations

Abbreviation	Meaning
2 hr. PG	2-hour plasma glucose
ACF	Auto-correlation Coefficient Function
Adam	Adaptive momentum estimation
AGP	Ambulatory Glucose Profile
AID	Automated insulin delivery
AMP	Adenosine Monophosphate
AMPK	AMP- activated protein kinase
ANN	Artificial Neural Network
ASCVD	Atherosclerosis cardiovascular disease
ATTD	Advanced technologies and treatment for diabetes
BG	Blood glucose
BGM	Blood glucose monitoring
BMI	Body mass index
CBG	Capillary blood glucose
CGM	Continuous glucose monitoring
CKD	Chronic kidney disease
CNN	Convolutional Neural Network
COD	Coefficient of determination
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complication Trial
DiaDRIL	Diabetes Data Registry and Individualized Lifestyle Intervention
DKA	Diabetic Ketoacidosis
DL	Deep learning
DM	Diabetes Mellitus
DPP4	Dipeptidyl peptidase 4
ECG	Electrocardiography
FCN	Fully Convolutional Network

FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GIP	Gastric inhibitory polypeptide
GLP1	Glucagon like peptide 1
GLUT	Insulin responsive glucose transporter
GRU	Gated recurrent unit
HbA1c	Glycosylated Hemoglobin
HDL	High-density lipoprotein cholesterol
HF	Heart Failure
ICONIP	International Conference on Neural Information processing
ICR	Insulin to carbohydrates ratio
IDDM	Insulin-dependent Diabetes Mellitus
ISF	Insulin sensitivity factor
KATP	ATP sensitive potassium channels
LAA	Long-Acting Insulin Analog
LADA	Latent Autoimmune Diabetes of Adults
LDL	Low-density lipoprotein cholesterol
LM	Last Measurement
LSTM	Long Short-Term Memory
MAE	Mean Absolute Error
MDI	Multiple Daily injections
MLP	Multilayer Perceptron
MODY	Maturity Onset Diabetes of the Young
MSE	Mean Square Error
NGSP	National Glycohemoglobin Standardization Program
NIDDM	Non-insulin dependent Diabetes Mellitus
N	Neutral Protamine Hagedorn Insulin
NPH	Neutral Protamine Hagedorn Insulin
OGTT	Oral Glucose Tolerance Test
PACF	Partial Autocorrelation Function
PH	Prediction Horizon
PPARɣ	Peroxisome proliferator Activated Receptor Agonist

R	Regular human insulin
RAA	Rapid Acting Insulin Analog
ReLU	Rectified linear unit
RMSE	Root Mean Square Error
RNN	Recurrent Neural Network
ROC-AUC	Receiver operating curve-Area under curve
SD	Standard deviation
SGLT2	Sodium Glucose Cotransporter 2
SGD	Stochastic Gradient Descent
SMBG	Self-monitoring blood glucose
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TAR	Time Above Range
TBR	Time Below Range
TDD	Total Daily Dose
TimeGAN	Timeseries Generative Adversial Network
TIR	Time In Range
URAA	Ultra Rapid Acting Insulin Analogs
WHO	World Health Organization

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Abstract

Background: Diabetes Mellitus (DM) is a chronic metabolic disorder that results in abnormal blood glucose regulation. People with diabetes are prone to develop devastating long-term complications including cardiovascular disease, neuropathy, retinopathy, renal failure and even mortality. Keeping blood glucose in near normal levels and normalizing patients' HbA1c leads to a lower frequency of macrovascular and microvascular complication. Due to this, blood glucose monitoring plays a vital key in diabetes care. Especially, Continuous Glucose Monitoring (CGM) which monitors interstitial blood glucose in real time. However, the huge amount of data obtained from CGM sensors requires finding ways to analyze the data more efficiently. Thus, using artificial intelligence and deep learning models to better interpret these results. Further using deep learning models like RNNs based on Long Short-Term Memory (LSTM) networks that has been designed for time sequence prediction problems has enabled researchers to propose specialized models to predict future values of blood glucose based on patient's existing data.

Aim: The main purpose of this study is to use artificial intelligence to better analyze patients' CGM data. In addition to using a deep learning model based on LSTM neural network to predict future trends in patients' data and help prevent either hyperglycemia or hypoglycemia episodes from occurring in order to improve the patient's treatment plan and their life quality.

Materials and Methods: This study utilized the Shanghai_T1DM and Shanghai_T2DM datasets. The data was collected from Diabetes Data Registry and Individualized Lifestyle Intervention (DiaDRIL) was initiated in Shanghai East Hospital and Shanghai Fourth People's Hospital affiliated to Tongji University since 2019. The data contains 3 to 14 days of CGM data corresponding to 12 patients with T1DM and 100 patients with T2DM, respectively. Some patients might have multiple periods of CGM recordings. The CGM data was analyzed using artificial intelligence to find each dataset's characterizations. Furthermore, we calculated the autocorrelation function (ACF) and the time percentage of TAR, TBR and TIR for patients in both datasets. Later, we mapped the data onto risk scores and used a RNN based neural network to predict future values of blood glucose.

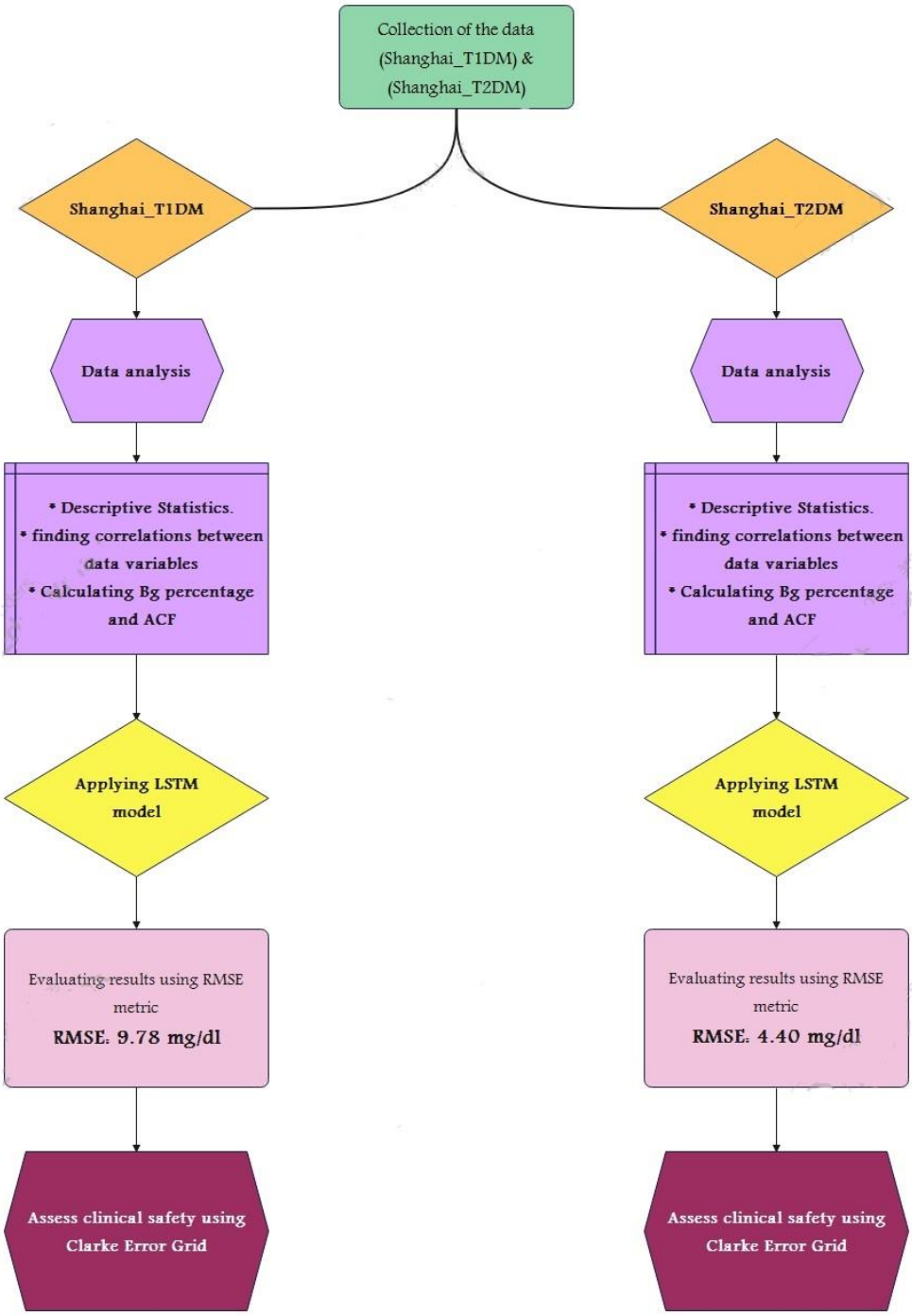
Results: After applying the model to both Shanghai_T1DM and Shanghai_T2DM we evaluated the model performance using the Root Mean Square Error (RMSE) metric. We achieved a result of (RMSE: 9.78 mg/dl) for the LSTM model in T1DM patients' data and (RMSE: 4.40 mg/dl) in T2DM patients' data. Overall, our models demonstrated high prediction accuracy, supported by low RMSE values. But the model performed better in T2DM with a lower RMSE than that of T1DM. Moreover, we assessed the clinical safety of glucose prediction using the Clarke Error Grid (CEG). In T1DM data, most of the predictions fell in zones A or B which are either accurate of clinically benign with very few predictions were inaccurate or could be clinically harmful. Alternatively, in T2DM

data most of the predictions were in zone A which is clinically accurate while the rest of the predictions were in Zone B which is clinically benign.

Conclusion: In this study, we show that our LSTM model was able to accurately and safely predict glucose values. In addition, translation of our prediction models to individuals with both type 1 diabetes showed encouraging results. We observed high precision in predictions. As such, the prediction model can be used to improve closed-loop insulin delivery systems by overcoming sensor delay. In addition, longer prediction intervals may be used to safely bridge periods of sensor malfunction. On another note, analyzing CGM data in T2DM and accurately predicting patient's glucose at different intervals offers an immense help in improving the drug choices based on the trends in the data. Potential future research avenues could involve the inclusion of meals and insulin doses delivered to the patient in the model in order to computationally decide the optimal dose of insulin needed independent of patient's input.

Keywords: Endocrinology; Diabetes Mellitus; CGM; Artificial intelligence; Deep Learning; Neural Networks; LSTM

Research diagram flowchart



Chapter 1: The theoretical framework of the thesis

1.1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that results in abnormal blood glucose (BG) regulation, mostly either due to the dysfunction of pancreatic β-cells responsible for the production of insulin. This hormone regulates the BG concentration by allowing cells and tissues to absorb glucose from the bloodstream (Type I) thus requiring lifelong exogenous insulin treatment, or the inability of the body to respond to endogenous insulin causing insulin resistance and relative insulin deficiency (type II) and various subtypes including Maturity-onset diabetes of the young (MODY) and Latent autoimmune diabetes of adults (LADA) [1].

People with diabetes are prone to an increased morbidity and mortality rate as compared to the normal population [2]. Diabetes induced hyperglycemia could lead to increasingly devastating complications long term, including cardiovascular disease, neuropathy, retinopathy, kidney failure and even mortality [3,4]. The prevalence of diabetes has been increasing rapidly over the past few decades. In 2019, about 463 million adults (9.3%) worldwide were living with diabetes, while it is estimated to be 578 (10.2%) and 700 (10.9%) million by 2030 and 2045, respectively [5]. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Another 460 000 kidney disease deaths were caused by diabetes [6], and raised blood glucose causes around 20% of cardiovascular deaths [7].

It is shown that the available antidiabetic treatments combined with a near-to-normal glucose levels approach, indicating the efforts of reducing high glucose levels and normalizing glycated hemoglobin (HbA1c) levels in the absence of any contraindications, may lead to a lower frequency of DM related microvascular and macrovascular events and all-time mortality in T1DM and T2DM [3,4]. On the other hand, intensified treatment targeting towards an intensive glucose control is associated with a higher risk of therapy-induced hypoglycemia and severe hypoglycemic events, which pose a potential risk for worsening or developing major macrovascular and

microvascular complications, serious neurological consequences, as well as cardiovascular and all-cause mortality [8,9,10,11]. Additionally, hypoglycemia is a severe adverse outcome that may negatively impact a patient's health and psychological status, leading to poor compliance and treatment adherence [10,11].

Hypoglycemic events are also associated with a high direct and indirect cost for patients, healthcare systems, and society [11,12]. Thus, the accurate prediction of blood glucose variations and, in particular, hypoglycemic events is of paramount importance to avoid potential detrimental complications and adjust the therapeutic strategy in a more optimized and personalized treatment strategy for patients with DM.

Due to this, Blood glucose measurement plays a vital key part in diabetes care, which allows patients to adjust their food intake, physical activity and medications with the help of physicians in order to maintain normoglycemia.

Self-monitoring of blood glucose (SMBG) is a measurement that uses blood to collect blood glucose information at many time points [13]. Recently, a continuous glucose monitoring (CGM) technology is used to continuously monitor the BG levels in more or less real time [14,15]. Furthermore, emerged evidence has also emphasized the importance of avoiding fluctuations in glycemia in DM [16]. Of note, the Advanced Technologies & Treatments for Diabetes (ATTD) consensus recommendations highlight the role of glycemic variability and the time in ranges (including the time in target range, hyperglycemia, and hypoglycemia) as key metrics for Continuous Glucose Monitoring (CGM) [17]. The use of CGM technology makes it possible to obtain a huge amount of continuous BG data which requires more advanced techniques for analysis and discovering better ways to integrate these results into adjusting patients' treatment plan.

Recently, machine learning techniques—due to their adaptive nature in a world with dynamic environments and knowledge—have been successful at solving complex tasks that are difficult to model with other classical approaches. With their efficacy in in solving classification and regression problems, and the ever-growing availability of already collected personal data makes the prediction of diabetic blood glucose through data-driven approaches possible [18,19,20]. Machine learning-based data-driven approaches use the individual's recorded data. Blood glucose dynamics in

patients with DM are affected by factors such as pancreatic function, insulin levels, carbohydrate intake, history of poor glycemic and the level and extent of physical activity. Models using combinations of input parameters accounting for these factors have been previously considered [21,22]. On account of its predictive effectiveness, deep learning has quickly become quite effective in blood glucose prediction. Among different deep-learning approaches, RNNs based on the long short-term memory (LSTM), have been designed for sequence prediction problems and are the most commonly used models [21,23-29].

In this study we propose a DL model to help predict future CGM values in individual patients' data in order to help avoid either hyperglycemia or hypoglycemia episodes.

1.2. Research Problem:

Patients' glucose levels vary during the day, therefore CGM is used to monitor these levels and give a better understanding of the condition of the patients and how to better improve their treatment plan. The main obstacle with CGM is that it provides an enormous amount of data which makes it harder to interpret manually.

1.3. Aim of study:

The main purpose of this study is to use artificial intelligence to better analyze patients' CGM data. In addition to using a deep learning model based on LSTM neural network to predict future trends in patients' data and help prevent either hyperglycemia or hypoglycemia episodes from occurring in order to improve the patient's treatment plan and their life quality.

1.4. Study hypothesis

Glucose forecasting by using CGM – a time sequence data- in order to predict future trends and prove autocorrelation of CGM data.

1.5. Limitations

- CGM sensors are rather expensive thus limiting the amount of data available for analysis and rather inaccessible for public use.

- the dataset of each patient is often too small to train a patient-specific deep-learning model.
- the dataset is usually highly imbalanced given that hypo- and hyperglycemic episodes are usually much less common than normoglycemia.

Chapter 2: Reference Studies

2.1. First Study:

"Chinese diabetes datasets for data-driven machine learning" [30]

A study conducted by Qinpei Zhao et. al. at Tongji University, Shanghai, China. (2023). The primary objective of this study was to provide more extensive dataset on both patients of type 1 and type 2 diabetes mellitus that can contribute to the development of data-driven algorithms/models and diabetes monitoring/managing technologies. Considering the data already available in literature which is mostly patients of type 1 DM. this data includes ShanghaiT1DM and ShanghaiT2DM Datasets and made them publicly available for research purposes. This paper describes the datasets, which was acquired on Type 1 (n = 12) and Type 2 (n = 100) diabetic patients in Shanghai, China. The acquisition has been made in real-life conditions, the patients were recruited from in Shanghai East Hospital (September 2019 to March 2021) and Shanghai Fourth Peopleś Hospital (June 2021 to November 2021), respectively. The datasets contain the clinical characteristics, duration of diabetes, laboratory measurements, complications and medications of the patients. Moreover, the continuous glucose monitoring readings with 3 to 14 days as a period together with the daily dietary information are also provided. The authors analyzed the properties of the available data as well as comparing it with previously publicly available CGM datasets like OhioT1DM, D1NAMO etc... furthermore, the authors analyzed the use of an autocorrelation function (ACF) and partial autocorrelation function (PACF) in conjunction in order to select the appropriate time-series models, e.g., ARIMA to help prevent hypoglycemia and hyperglycemia events. This study provided the first publicly available datasets to include rich information for people with T1DM and T2DM in China. With hope that the datasets could contribute to the research in data-driven machine learning.

2.2. Second Study:

"Prediction of Blood Risk Score in Diabetes Using Deep Neural Networks" [31]

This study was conducted by J. Quetzalcóatl Toledo-Marín et al. at University of British Colombia, BC Children's Hospital Research Institute in Vancouver, Canada. The aim of this study was to improve the prediction of blood glucose thus improving the quality of life of people living with type 1 diabetes by enabling them to better manage their care. Given the anticipated benefits of such a prediction, the authors rather than attempting to predict glucose concentration, they used a deep learning framework for prediction in which prediction is performed using a scale for hypo- and hyper-glycemia risk. Using the blood glucose risk score formula proposed by Kovatchev et al., models with different architectures were trained, including, a recurrent neural network (RNN), a gated recurrent unit (GRU), a long short-term memory (LSTM) network, and an encoder-like convolutional neural network (CNN). The authors trained the models using The OpenAPS Data Commons data set, comprising 139 individuals, each with tens of thousands of continuous glucose monitor (CGM) data points. To evaluate these predictions, performance results are compared with the last measurement (LM) prediction. The results obtained are competitive when compared to other deep learning methods. A root mean squared error (RMSE) of 16 mg/dL, 24 mg/dL, and 37 mg/dL were obtained for CNN prediction horizons of 15, 30, and 60 min, respectively. However, no significant improvements were found for the deep learning models compared to LM prediction. Performance was found to be highly dependent on architecture and the prediction horizon. This paper proposed new deep learning prediction framework by using a hypo- and hyperglycemia risk-score scale rather than attempting to predict glucose concentrations, leading to more robust training.

2.3. Third Study:

"Prediction-Coherent LSTM-based Recurrent Neural Network for Safer Glucose Predictions in Diabetic People" [32]

This study was conducted by Maxime De Bois et al. and published as part of International Conference on Neural Information Processing (ICONIP 2019: Neural Information Processing) on 2019. The authors proposed in the context of time-series forecasting, a LSTM-based recurrent neural network architecture and loss function that enhance the stability of the predictions.

The data used comes from two distinct datasets: the Ohio T1DM dataset and the IDIAB dataset accounting for 6 type 1 and 5 type 2 diabetic patients respectively. First, the authors of this study confirm the superiority -in the context of glucose prediction- of the LSTM model by comparing it to other state-of-the-art models (Extreme Learning Machine, Gaussian Process regressor, Support Vector Regressor). Then, they show the importance of making stable predictions by smoothing the predictions made by the models, resulting in an overall improvement of the clinical acceptability of the models at the cost in a slight loss in prediction accuracy. Finally, they show that the proposed approach, outperforms all baseline results. More precisely, it trades a loss of 4.3% in the prediction accuracy for an improvement of the clinical acceptability of 27.1%. When compared to the moving average post-processing method, the study shows that the trade-off is more efficient with this approach. This study offered a comprehensive comparison between different artificial intelligence models and provides a basis for further research in developing these models and implementing them in medical practice in order to better improve patients' treatment plan in the future.

2.4. Fourth Study:

"Therapy-driven Deep Glucose Forecasting" [33]

This study was conducted by Eleonora Maria Aiello et al. and was published in "Engineering Applications of Artificial Intelligence" journal in January 2020. The data used in this study was an in-silico dataset that has been generated using the UVA/Padova simulator (n=100), which is equipped with a cohort of virtual patients and accepted by Food and Drug Administration (FDA) as a substitute to animal trials. In this paper the authors propose Deep Glucose Forecasting, a deep learning approach for forecasting glucose levels, based on a novel, two-headed Long-Short Term Memory implementation. It takes in input the previous values obtained through continue glucose monitoring, the carbohydrate intake, the suggested insulin therapy and forecasts the interstitial glucose level of the patient. The deep learning model used is based on stacked Long Short-Term Memory (LSTM) cells which are able to learn how to filter part of their hidden state during the inference process in order to model long-term temporal dependencies. The training process uses a Mean Squared Error loss function (MSE) with a default Adam optimizer. The model is trained using the in-silico dataset then

tested on another in-vivo dataset (a 1-month dataset containing all the data collected during the clinical trial for a single patient). thus, the model obtained considering this additional information is able to generalize to new unseen data and improve the overall glucose control. The predictions of the model are evaluated in terms of Coefficient of Determination (COD), the index of fitting called FIT, and Root Mean Square Error (RMSE). The Deep Glucose Forecasting model scores (COD:69.85%, FIT: 48.44%) which after fine tuning improve to (COD:84.05%, FIT:60.14). and error rate (RMSE: 27.29) that drops to (RMSE: 21.09) after fine tuning. The proposed model in this paper is able to generalize to new unseen data, outperforms classical population models and reaches performance comparable to classical personalized models when fine-tuning is exploited on real patients. such deep learning models help with predicting future glucose levels and alter insulin therapy in order to define the optimal treatment.

2.5. Fifth Study:

"Deep transfer learning and data augmentation improve glucose levels prediction in type 2 diabetes patients" [34]

A study conducted by Yixiang Deng et al. and was published in "Digital medicine" in 2021. The aim of this research is to develop deep-learning methods to predict patient-specific blood glucose during various time horizons in the immediate future using patient-specific every 30-min long glucose measurement by the continuous glucose monitoring (CGM) to predict future glucose levels in 5 min to 1 h. the dataset used in this paper is public dataset OhioT1DM. the two main problems that this paper aims to solve is imbalanced data (as normoglycemic levels are more common than hyperglycemic or hypoglycemic) and the fact that each patient data is too small to train any model. This study utilizes the use of CNN, RNN (LSTM in particular) in addition to mixup (beyond empirical risk Minimization) and time-series generative adversarial networks (TimeGAN) and later suggested their best model (CNN +Transfer2) outperforms all other models in terms of mean absolute error (MAE). Therefore, to solve the problem of imbalanced data in CGM dataset this study uses data augmentation by fixing the loss function in the model to be the relative mean absolute error (REL. MAE) and comparing the performance of the model when four different data pre-processing techniques are implemented for data augmentation on the training

data of the minority class and a prediction horizon at 20 min. For this data augmentation method, the authors repeated the minority samples (the input-output pairs where the output BG is less than 80 mg/dL) in the training dataset for k folds. And by using TimeGAN they generated synthetic minority samples that where further used in this model. The other issue raised by this paper is the difficulty of obtaining a sufficient large dataset for each patient, thus, the authors applied "Transfer learning" by pre-training the networks on other patients' data by excluding the data from the target patient, and then further fine-tuning the network on one part of the target patient's data. Finally, they test the network on the rest of the data from the target patient. The applied model achieved an Accuracy of 95.98%, sensitivity of 59.19% and specificity of 98.15%. the study proposed a new combined approach of transfer learning and data augmentation for imbalanced data can be proved a very powerful new framework for short term predictions for type 2 diabetes.

2.6. Sixth Study:

"Data-driven modeling and prediction of blood glucose dynamics: Machine learning applications in type 1 diabetes" [35]

This paper was published in "Artificial Intelligence in Medicine" in 2019 by Ashenafi Zebene Woldaregay et al. the main purpose of this review was to develop a compact guide regarding modeling options and strategies

of machine learning and a hybrid system focusing on the prediction of BG dynamics in type 1 diabetes. The review covers machine learning approaches pertinent to the controller of an artificial pancreas (closed-loop systems), modeling of personalized profiles, personalized decision support systems, and BG alarm event applications. This paper provides a comparison between literature available on the use of machine learning in type 1 diabetes based on various categories including (Age and Number of Subjects, Type of Input, Data Format or Type/Data Source/Data Size, Input Preprocessing, Class of Machine Learning, Training/Learning Algorithm, Validation techniques, Prediction Horizon (PH) and Performance Metrics/Evaluation Criteria). Various machine learning techniques have been tested to predict BG, such as, recurrent neural networks, feed-forward neural networks, support vector machines, self-organizing maps, Gaussian

processes, genetic algorithms and programming, and deep neural networks. These techniques use various groups of input parameters and training algorithms. The main limitation of the current approaches is the lack of a well-defined approach to estimate carbohydrate intake, which is mainly done manually by the individual users and is prone to an error that can severely affect the predictive performance. Moreover, there is the lack of a universal approach to estimate and quantify the approximate effect of physical activities, stress, and infection incidence on the BG level. Almost all the studies have quite different approaches, and this poses a challenge in terms of regarding one approach as universal. None of the researchers have assessed model predictive performance during stress and infection incidences in a free-living condition, which should be taken into account in future studies. Furthermore, little has been done regarding model portability that can capture the inter- and intra-variations among patients. It seems that the effect of time lags between the CGM reading and the actual BG levels is also not well covered. However, in general, we foresee that these developments might foster the next generation of BG prediction, which should result in a great contribution in the effort to develop the long-awaited so-called artificial pancreas (a closed-loop system).

Chapter 3: Theoretical background on Diabetes Mellitus

3.1. Diabetes Mellitus:

Diabetes mellitus (DM) is a chronic metabolic disorder that results in abnormal blood glucose (BG) regulation, mostly either due to the failure of the body to secrete insulin (Type I) or the inability of the body to respond to insulin action (type II). Insulin, is the hormone responsible for the storage of prandial glucose as glycogen in the liver thereby lowering blood glucose levels. Hyperglycemia leads overtime to developing major macrovascular and microvascular complications, serious neurological consequences, as well as cardiovascular and renal complications. People with diabetes are prone to an increased morbidity and mortality rate as compared to the normal population [2]. The prevalence of diabetes has been increasing rapidly over the past few decades. In 2019, about 463 million adults (9.3%) worldwide were living with diabetes, while it is estimated to be 578 (10.2%) and 700 (10.9%) million by 2030 and 2045, respectively [5]. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes occurred before the age of 70 years. Another 460,000 kidney disease deaths were caused by diabetes [6], and raised blood glucose causes around 20% of cardiovascular deaths [7].

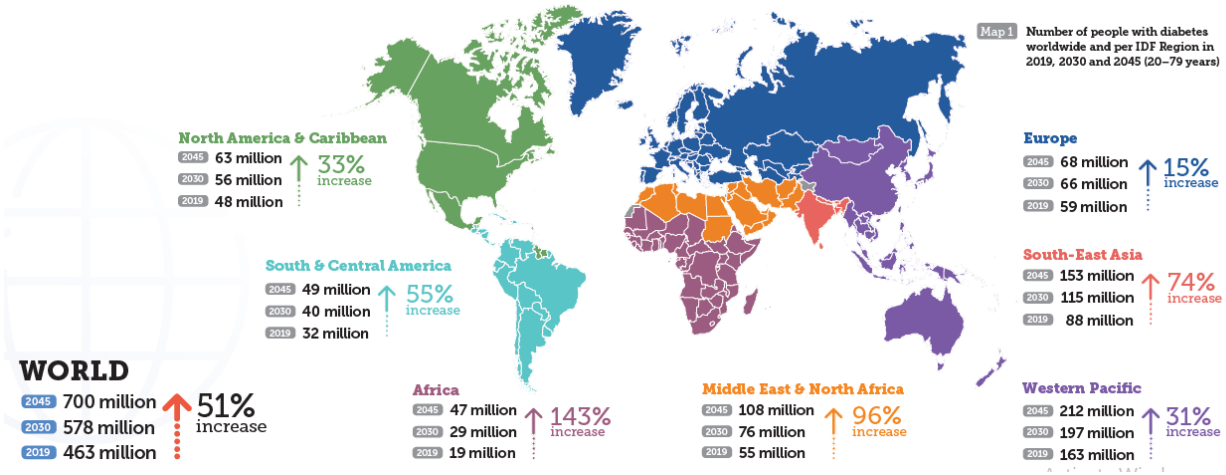


Figure 3.1. prevalence of Diabetes Mellitus around the world in 2019 with comparison to expected numbers in 2030 and 2045.

3.2. Physiology of insulin

The human insulin gene resides on the short arm of chromosome 11. A unique set of transcription factors found in the β cell nucleus activates the transcription of the preproinsulin mRNA from the insulin gene (Figure 3.2.). A precursor molecule, preproinsulin, a peptide of MW 11,500, is translated from the preproinsulin messenger RNA in the rough endoplasmic reticulum of pancreatic β cells (see Figure 3.3.). Microsomal enzymes cleave preproinsulin to proinsulin almost immediately after synthesis. Proinsulin is transported to the Golgi apparatus, where packaging into clathrin-coated secretory granules takes place. Maturation of the secretory granule is associated with loss of the clathrin coating and conversion of proinsulin into insulin and a smaller connecting peptide, or C peptide, by proteolytic cleavage at two sites along the peptide chain. Mature secretory granules contain insulin and C peptide in equimolar amounts and only small quantities of proinsulin, a small portion of which consists of partially cleaved intermediates [36,37].

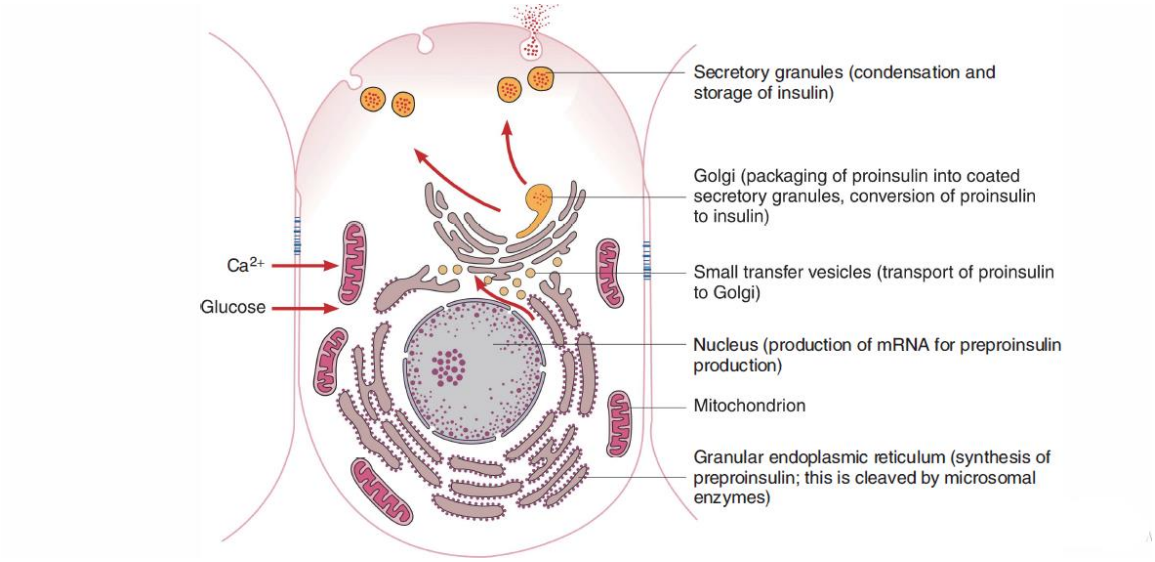


Figure 3.2. Structural com ponents of the pancreatic β cell involved in glucose-induced biosynthesis and release of insulin.

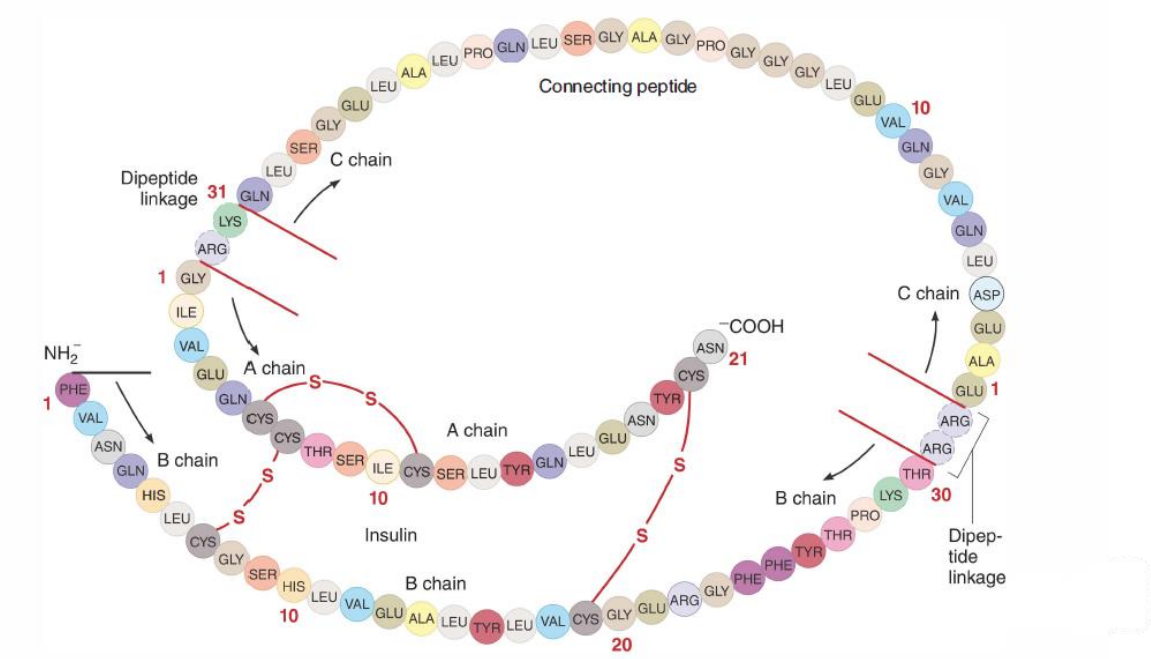


Figure 3.3. Structure of human pro-insulin C peptides and insulin molecules connected at two sites by dipeptide links.

3.3. Diabetes Mellitus Diagnosis

Diabetes maybe diagnosed based on Plasma glucose criteria, either the fasting plasma glucose (FPG) value or the 2-h plasma glucose(2-hPG) value during a 75-g oral glucose tolerance test (OGTT) or A1C criteria. The following criteria is used to diagnose DM according to the 2024 Diabetes Care issue proposed by the American Diabetes Association [1]:

Criteria for the diagnosis of DM
A1C ≥ 6.5% (48mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay. *
Or
FPG ≥ 126 mg/dL (7.0mmol/L). Fasting is defined as no caloric intake for at least 8h.*
Or
2-h PG ≥ 200 mg/dL (11.1mmol/L) during OGTT. The test should be performed as described **b**y WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. *
Or
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1mmol/L).

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; NGSP, National Glycohemoglobin Standardization Program; WHO, World Health Organization; 2-hPG, 2-h plasma glucose. * In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Table 3.1. Criteria for the diagnosis of DM according to the American Diabetes Association's Diabetes Care Journal 2024.

3.4. Diabetes Mellitus Classification

Diabetes is classified into five main groups based on known pathological and etiologic mechanisms-type 1, type 2, monogenic, secondary, and gestational diabetes (Table 3.2).

I. Type 1 Diabetes[a] (β cell destruction, usually leading to absolute insulin deficiency)
- A. Immune-mediated, type 1a
- B. Idiopathic, type 1b

II. Type 2 Diabetes[a] (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with minimal insulin resistance)

III. Monogenic Diabetes
- A. Autosomal dominant genetic defects of pancreatic β cells
  1. Maturity onset diabetes of the young (MODY)
  2. Insulin gene (*INS*)
  3. ATP-sensitive potassium channel (*KCNJ11* and *ABCC8*)
- B. Other genetic defects of pancreatic β cells
  1. Autosomal recessive genetic defects
  2. Mitochondrial DNA
  3. Ketosis-prone diabetes (KPD)
- C. Genetic defects in insulin action
  1. Insulin receptor mutations
  2. Lipoatrophic diabetes
- D. Neonatal diabetes (overlaps with categories A, B, C, E, and F)
  1. Transient
  2. Permanent
- E. Monogenic autoimmune syndromes
  1. IPEX: Immunodysregulation polyendocrinopathy enteropathy, X-linked
  2. Autoimmune polyendocrinopathy syndrome type 1
  3. Other autosomal recessive autoimmune polyendocrinopathies (*IL2RA*, *ITCH*, and *LRBA*)
  4. Other autosomal dominant autoimmune polyendocrinopathies (*STAT1*, *STAT3*, and *SIRT1*)
- F. Other genetic syndromes sometimes associated with diabetes
  1. Chromosomal defects: Down, Klinefelter, and Turner syndromes
  2. Neuromuscular syndromes: Friedreich ataxia, Huntington chorea, myotonic dystrophy, porphyria, and others
  3. Obesity syndromes: Laurence-Moon-Biedl, Bardet-Biedl, Prader-Willi syndromes, and others
  4. Wolfram syndrome

IV. Secondary Diabetes
- A. Diseases of the exocrine pancreas
  1. Pancreatitis
  2. Trauma, pancreatectomy
  3. Neoplasia
  4. Cystic fibrosis
  5. Hemochromatosis
  6. Fibrocalculous pancreatopathy
- B. Endocrinopathies
  1. Acromegaly
  2. Cushing syndrome
  3. Glucagonoma
  4. Pheochromocytoma
  5. Hyperthyroidism
  6. Somatostatinoma
  7. Aldosteronoma
- C. Drug- or chemical-induced
  1. β cell toxicity: vacor, pentamidine, cyclosporine
  2. β cell autoimmunity: α-interferon, anti-PD-1, anti-PD-L1, anti-CTLA-4
  3. β cell dysfunction: thiazide and loop diuretics, diazoxide, α agonists, β blockers, phenytoin, opiates
  4. Insulin resistance: glucocorticoids, progesterone, nicotinic acid, thyroid hormone, β blockers, atypical antipsychotic drugs, antiretroviral protease inhibitors
- D. Infections
  1. Congenital rubella
  2. Other viruses: cytomegalovirus, coxsackievirus B, adenovirus, mumps
- E. Uncommon forms of immune-mediated diabetes
  1. Stiff-person syndrome
  2. Anti-insulin receptor antibodies
  3. POEMS syndrome

V. Gestational Diabetes Mellitus (GDM)

Table 3.2 Etiologic classification of DM.

3.4.1 Type 1 Diabetes Mellitus

Type 1 diabetes is immune-mediated in more than 95% of cases (type 1a) and idiopathic in less than 5% (type 1b). It is a catabolic disorder in which circulating insulin is virtually absent, and the pancreatic β cells fail to respond to all known insulinogenic stimuli. In the absence of insulin, the three main target tissues of insulin (liver, muscle, and fat) not only fail to appropriately take up absorbed nutrients but continue to deliver glucose,

amino acids, and fatty acids into the bloodstream from their respective storage depots. Furthermore, alterations in fat metabolism lead to the production and accumulation of ketones. This inappropriate persistence of the fasted state postprandially can be reversed by the administration of insulin.

Latent autoimmune diabetes of adulthood (LADA) Type 1 diabetes can presents at any age, although peaks in incidence occur before school age and around puberty. Older adults often present with a more indolent onset that sometimes leads to misdiagnosis. These initially unrecognized patients may retain enough β cell function at the outset to avoid ketosis, but develop increasing dependence on insulin therapy over time as their β cell mass diminishes [37].

3.4.2 Type 2 Diabetes Mellitus

Type 2 diabetes mellitus results from relative insulin deficiency, in contrast to the absolute insulin deficiency of patients with type 1 diabetes. Type 2 diabetes is a heterogeneous disorder and probably represents a large number of different primary genetic and environmental insults leading to relative insulin deficiency. Clinically, patients with type 2 diabetes can range from those with severe insulin resistance and minimal insulin secretory defects to those with a primary defect in insulin secretion.

Type 2 diabetes accounts for 80% to 90% of cases of diabetes. These patients commonly present as adults with some degree of obesity. At onset, most patients with type 2 diabetes do not require insulin to survive, but over time their insulin secretory capacity tends to deteriorate, and many eventually need insulin treatment to achieve optimal glucose control [36, 37].

3.4.3. Monogenic Diabetes

Maturity-onset diabetes of the young (MODY), This subgroup of monogenic disorders is characterized by the onset of diabetes in late childhood or before the age of 25 years as a result of a partial defect in glucose-induced insulin release. A strong family history of early-onset diabetes occurring in one parent and in one-half of the parent's offspring suggests autosomal dominant transmission. In contrast to most patients with type 2 diabetes, these patients are generally nonobese and lack associated

insulin resistance. Instead, they exhibit predominantly a defect in glucose-stimulated insulin secretion. However, they are not ketosis-prone and may initially achieve good glycemic control without insulin therapy [37].

3.5. Diabetes Mellitus treatment

3.5.1. Diet

A well-balanced, nutritious diet remains a fundamental element of therapy for diabetes. It is recommended that the macronutrient proportions (carbohydrate, protein, and fat) be individualized based on the patient's eating patterns, preferences and goals. Limiting the carbohydrate intake and substituting some of the calories with monounsaturated fats, such as olive oil, can lower triglycerides and increase HDL cholesterol. A Mediterranean-style eating pattern has been shown to improve glycemic control and lower combined endpoints for cardiovascular events and stroke. Caloric restriction and weight loss is an important goal for the obese patient with type 2 diabetes.

Patients with type 1 diabetes or type 2 diabetes on insulin should be taught ***carbohydrate counting***, so they can administer their insulin bolus for each meal based on its carbohydrate content [36,37].

3.5.2. Agents for the treatment of hyperglycemia

These drugs are used for the treatment of T2DM and they fall into several different categories as follows [36,37,38];

1) **Drugs that act on the sulfonylurea receptor complex:**
    - ***Sulfonylureas:*** The sulfonylureas contain a sulfonic acid-urea nucleus that bind the ATP-sensitive potassium channels (KATr) on the surface of pancreatic β cells, resulting in closure of the channel and depolarization of the β cell. Thus, permitting calcium entrance the cell and actively promote insulin release. (First-generation sulfonylureas (tolbutamide, tolazamide, acetohexamide, and chlorpropamide, Second-generation sulfonylureas (glyburide, glipizide, gliclazide, and glimepiride))
    - ***Meglitinide Analogs:*** *Repaglinide* Acts by binding to the sulfonylurea receptor and closing the ATP-sensitive potassium channel. *Mitiglinide* is a benzylsuccinic acid derivative that

binds to the sulfonylurea receptor causing a brief pulse of insulin.

2) **Drugs that act on insulin target tissue:**
   - ***Metformin:***(1,1-dimethylbiguanide hydrochloride) is used, either alone or in conjunction with other oral agents or insulin. Metformin acts primarily through AMPK, which it activates by uncoupling mitochondrial oxidative phosphorylation and increasing cellular AMP levels. Metformin's therapeutic effects primarily derive from its effects on the liver, where it reduces hepatic gluconeogenesis and lipogenesis. Metformin is the first-line therapy for patients with type 2 diabetes. It is ineffective in patients with type 1 diabetes. A side benefit of metformin therapy is its tendency to improve both fasting and postprandial hyperglycemia and hypertriglyceridemia in obese patients with diabetes without the weight gain associated with insulin or sulfonylurea therapy.
   - ***Thiazolidinediones:***(Peroxisome-Proliferator-Activated Receptor Agonists), are insulin sensitizers exerting their antidiabetic effects through the activation of PPARɣ. Observed effects include increased GLUT expression (GLUT 1 and GLUT 4); decreased free fatty acid levels; decreased hepatic glucose output; and increased differentiation of preadipocytes into adipocytes. In addition to glucose-lowering, the thiazolidinediones have effects on lipids and other cardiovascular risk factors. (available drugs are: Rosiglitazone and Pioglitazone).

3) **Drugs that affect glucose absorption:**
   - ***Alpha-Glucosidase Inhibitors:*** These drugs are competitive inhibitors of intestinal brush border α glucosidases. These drugs delay the absorption of carbohydrates and reduce postprandial glycemic excursion. (Available drugs: Acarbose, Miglitol and Voglibose).

4) **Incretins:**
   - ***GLP-1 Receptor Agonists:*** The gut makes several incretins, gut hormones that amplify postprandial insulin secretion, including glucagon-like peptide-1. When GLP-1 is infused in patients with type 2 diabetes, it stimulates insulin secretion and lowers

glucose levels. (Semaglutide, Exenatide, Liraglutide, Albiglutide, Dulaglutide, and Lixisenatide are available for clinical use.)

- ***DPP4 Inhibitors:*** An alternative to the use of GLP-1 receptor agonists involves inhibition of the enzyme DPP-4 with prolongation of the action of endogenously released GLP-1 and GIP. (Sitagliptin, Saxagliptin, Linagliptin, Alogliptin and Vildagliptin are available for the treatment of type 2 diabetes).

5) Sodium Glucose Cotransporter 2 Inhibitors:

- ***SGLT2 inhibitors:*** Glucose is freely filtered by the renal glomeruli and is reabsorbed in the proximal tubules by the action of sodium-glucose cotransporters (SGLT). SGLT2 accounts for about 90% of glucose reabsorption and its inhibition causes glycosuria in people with diabetes, lowering plasma glucose levels. For people with type 2 diabetes and established ASCVD, HF, or CKD, an SGLT2 inhibitor has shown benefit in lowering primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or non-fatal stroke in addition to improving heart failure. Furthermore, SGLT2 inhibitors have shown primary evidence in slowing chronic kidney disease progression. (Available SGLT2 inhibitors: Canagliflozin, Dapagliflozin, Ertugliflozin and Empagliflozin).

3.5.3. Insulin

Insulin is indicated for individuals with type 1 diabetes as well as for those with type 2 diabetes whose hyperglycemia does not respond to diet therapy and other diabetes drugs. Insulin is available in different forms differing in duration of action and time to peak in action.

Human insulin is dispensed as either regular (R) or Neutral Protamine Hagedorn (NPH) formulations. Six analogs of human insulin- three rapidly acting (insulin lispro, insulin aspart, and insulin glulisine) and three long-acting (insulin glargine, insulin detemir, and insulin degludec) are available for clinical use [36,37,38].

TABLE **Insulin Types and Action Profiles**

	Product	Onset of Action	Peak Action	Duration
Rapid acting	Aspart (*Novolog* [Novo Nordisk, Princeton, NJ]) Lispro (*Humalog U-100* [Eli Lilly, Indianapoils, IN], *Humalog U-200* [Eli Lilly, Indianapoils, IN], *Admelog* [Sanofi, Bridgewater, NJ]) Glulisine (*Apidra* [Sanofi, Bridgewater, NJ]) Aspart (*Fiasp* [Novo Nordisk, Princeton, NJ]) Insulin human (*Afrezza* [MannKind, Westlake Village, CA]) inhalation powder	10–30 min 2.5 min 12 min	30–180 min 40–50 min 35–45 min	3–5 h 1.5–3 h
Short acting	Regular U-100 (Humulin R U-100 [Eli Lilly, Indianapolis, IN]) Regular U-100 (Novolin R [Novo Nordisk, Princeton, NJ]) Regular U-500 (Humulin U-500)	30–60 min	2–4 h	U-100: Up to 10 h U-500: Up to 24 h
Intermediate Acting	NPH (Humulin N) NPH (Novolin N)	2–4 h	4–8 h	12–18 h
Long Acting	Detemir (*Levemir* [Novo Nordisk, Princeton, NJ]) Glargine (*Lantus* [Sanofi, Bridgewater, NJ], *Basaglar* [Eli Lilly, Indianapoils, IN], *Toujeo U-300* [Sanofi, Bridgewater, NJ]) Degludec (*Tresiba U-100* [Novo Nordisk, Princeton, NJ], *Tresiba U-200*)	2–4 h	Minimal	Detemir: 12–24 h Glargine: up to 24 h Degludec: up to 48 h
Premixed	70/30 (NPH/Aspart) (*Novolog 70/30*) 70/30 NPH/Regular (*Humulin 70/30*) 75/25 (NPH/Lispro) (*Humalog 75/25*) 50/50 (NPH/Lispro) (*Humalog 50/50*) [Other combinations may be available in Europe.]	5–60 min	Dual	12–18 h

Table 3.3. Insulin types and action profiles.

1) **Short Acting Insulin Preparation:**
   - ***Regular insulin:*** is a short-acting, soluble crystalline zinc insulin whose hypoglycemic effect appears within 30 minutes after subcutaneous injection, peaks at about 2 hours, and lasts for about 5-7 hours. It's the only insulin that can be used intravenously and is particularly useful in the treatment of Diabetic ketoacidosis and during the perioperative management of diabetics.
   - ***Rapidly acting insulin analogs:*** are modified human insulin they're characterized by their Rapid absorption, faster action and shorter duration. When injected subcutaneously, they have an onset of action at 15 minutes and they peak at 1 hour and last approximately for 2-4 hours. (Available short acting insulin analogs are: Lispro, Aspart, Glulisine).
2) **Long-Acting Insulin Preparations:**
   - ***Neutral Protamine Hagedorn (NPH):*** is an intermediate-acting insulin in which the onset of action is delayed by combining two parts of soluble crystalline zinc insulin with one part protamine zinc insulin. Its onset of action is delayed by 2-4 hours, and its peak response is generally reached in about 8-10 hours and its duration of action is often less than 24 hours (with a range of 10-20 hours).

- ***Insulin Glargine:*** is an insulin analog in which the asparagine at position 21 of the A chain of the human insulin molecule is replaced by glycine and two arginines are added to the carboxyl terminal of the B chain. It lasts for about 24 hours without any pronounced peaks and is given once a day to provide basal coverage. When this insulin was given as a single injection at bedtime to type 1 diabetes patients, fasting hyperglycemia was better controlled when compared with bedtime NPH insulin.
- ***Insulin detemir:*** is an insulin analog in which the threonine at position 30 of the B chain has been removed and a 14-C fatty acid chain (tetradecanoic acid) is attached to the lysine at position 29 by acylation. The duration of action for insulin detemir is about 17 hours with minimal peaks.
- ***Insulin degludec:*** In this insulin analog, the threonine at position B30 has been removed and the lysine at position B29 is conjugated to hexadecanoic acid via a gamma-Lglutamyl spacer.

3) Insulin Mixtures:

Patients with type 2 diabetes can sometimes achieve reasonable glucose control with just prebreakfast and pre-supper injections of mixtures of short acting and NPH insulins. Stable premixed insulins ***(70% NPH and 30% regular)*** are available as a convenience to patients who have difficulty mixing insulin because of visual problems or insufficient manual dexterity.

With increasing use of rapid-acting insulin analogs as a pre-prandial insulin, it has become evident that combination with an intermediate-acting or long-acting insulin is essential to maintain postabsorptive glycemic control. Premixed combinations of NPL (neutral protamine lispro) and insulin lispro are now available for clinical use ***(Humalog Mix 75/25 and Humalog Mix 50/50).*** These mixtures have a more rapid onset of glucose-lowering activity compared with 70% NPH/30% regular human. Similarly, a 70% insulin aspart protamine/30% insulin aspart ***(NovoLogMix 70/30)*** is now available. The main advantages of these new mixtures are that (1) they can be given within 15 minutes of starting a meal and (2) they are superior in controlling the postprandial glucose rise after a carbohydrate-rich meal.

The longer-acting insulin analogs, insulin glargine or insulin detemir, cannot be acutely mixed with either regular insulin or the rapid-acting insulin analogs. Insulin degludec, however, can be mixed and is available ***as 70% insulin degludec/30% insulin aspart*** and is injected once or twice a day.

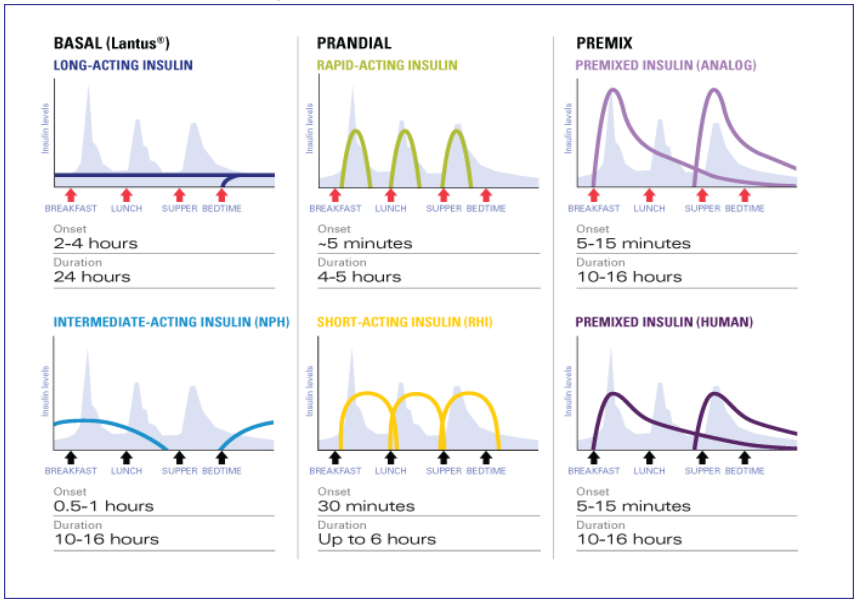


Figure 3.4. different types of insulin compaterive action.

Methods of insulin administration:

a typical starting dose is *0.3 to 0.5 units/kg per day*. Higher doses will be needed for individuals who are obese, children in puberty, or following presentation with DKA. This total daily dose (TDD) of insulin is typically given in a divided program of multiple daily injections (MDI). 50% of the TDD delivered as a once-daily dose of basal insulin while the other 50% given as boluses. There are several methods to administer insulin [38]:

1) ***Insulin Pump Therapy (hybrid closed-loop, low-glucose suspend):*** it offers a basal delivery of URAA or RAA; generally, 40–60% of TDD. And for mealtime and correction: URAA or RAA by bolus based on ICR and/or ISF and target glucose, with pre-meal insulin ~15 min before eating. The advantages of this pump are that it can adjust basal rates for varying insulin sensitivity by time of day, for exercise and for sick days. With additional flexibility in meal timing and content.
   While on the downside it's the most expensive regimen, the patient must continuously wear one or more devices. And more importantly

the risk of rapid development of ketosis or DKA with interruption of insulin delivery. There are also potential reactions to adhesives and site infections. And as it is the most technically complex approach (harder for people with lower numeracy or literacy skills).

2) ***MDI: LAA + flexible doses of URAA or RAA at meals***:
in this regimen the patient takes LAA once daily; generally, 50% of TDD. And for mealtime and correction: URAA or RAA based on ICR and/or ISF and target glucose. This regimen offers Flexibility in meal timing and content. Also, Insulin analogs cause less hypoglycemia than human insulins. As for this method's disadvantages: there is at least four daily injections. Furthermore, LAAs may not cover strong dawn phenomenon (rise in glucose in early morning hours) as well as pump therapy.
3) ***Four injections daily with fixed doses of NPH and RAA:***
(Pre-breakfast: RAA ~20% of TDD. Pre-lunch: RAA ~10% of TDD. Pre-dinner: RAA ~10% of TDD. Bedtime: N ~50% of TDD.)
This method may be feasible if patient is unable to carbohydrate count. All meals have RAA coverage. But shorter duration RAA may lead to basal deficit during day thus the patient may need twice-daily N. there is also greater risk of nocturnal hypoglycemia with N. plus it requires relatively consistent mealtimes and carbohydrate intake.
4) ***Four injections daily with fixed doses of NPH and R:***
(Pre-breakfast: R ~20% of TDD. Pre-lunch: R ~10% of TDD. Pre-dinner: R ~10% of TDD. Bedtime: N ~50% of TDD.)
This method is also more feasible if patient is unable to carbohydrate count. R can be dosed based on ICR and correction. And all meals have R coverage. But on the downside, there is a greater risk of nocturnal hypoglycemia with N. as well as greater risk of delayed post-meal hypoglycemia with R. it requires relatively consistent mealtimes and carbohydrate intake. R must be injected at least 30 min before meal for better effect.
5) ***Three injections daily: N+R or N+RAA:***
(Pre-breakfast: ~40% N + ~15% R or RAA. Pre-dinner: ~15% R or RAA. Bedtime: 30% N.)
This method may be appropriate for those who cannot take injections in middle of day. Also, Morning N covers lunch to some extent. It has the advantage of RAAs over R. the disadvantages of this method are a

greater risk of nocturnal hypoglycemia with N than LAAs, greater risk of delayed post-meal hypoglycemia with R than RAAs, it requires relatively consistent mealtimes and carbohydrate intake and coverage of post-lunch glucose often suboptimal. Plus, R must be injected at least 30 min before meal for better effect.

6) ***Twice-daily "split-mixed": N+R or N+RAA:***
(Pre-breakfast: ~40% N + ~15% R or RAA. Pre-dinner: ~30% N + ~15% R or RAA.)
This regimen offers the least number of injections for people with strong preference for this. Furthermore, it eliminates need for doses during the day. But on the other hand, there is a heightened risk of hypoglycemia in afternoon or middle of night from N. it needs a fixed mealtimes and meal content. The coverage of post-lunch glucose often suboptimal. Thereby it's difficult to reach targets for blood glucose without hypoglycemia.

Injected insulin regimens	Flexibility	Lower risk of hypoglycemia	Higher costs
MDI with LAA + RAA or URAA	+++	+++	+++
MDI with NPH + RAA or URAA	++	++	++
MDI with NPH + short-acting (regular) insulin	++	+	+
Two daily injections with NPH + short-acting (regular)insulin or premixed	+	+	+
Continuous insulin infusion regimens (Insulin pump)	+++++	+++++	+++++

Table 3.4. Insulin therapy regimen comparison.

3.6. Diabetes Mellitus Complications:

3.6.1. Acute DM complications:

3.6.1.1. Hypoglycemia:

Hypoglycemic reactions are the most common complications that occur in patients with diabetes who are treated with insulin. It can also occur in any patient taking oral agents that stimulate pancreatic β cells (e.g., sulfonylureas, meglitinide, δ-phenylalanine analogs), particularly if the patient is elderly and has renal or liver disease. The signs and symptoms of

hypoglycemia may be divided into those resulting from stimulation of the autonomic nervous system and those arising from neuroglycopenia (insufficient glucose for normal central nervous system function). When the blood glucose falls to around 54 mg/dL (3 mmol/L), the patient starts to experience both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger) nervous system symptoms. If these autonomic symptoms are ignored and the glucose levels fall further (to around 50 mg/dL [2.8 mmol/L]), then neuroglycopenic symptoms appear, including irritability, confusion, blurred vision, tiredness, headache, and difficulty speaking. A further decline in glucose (below 30 mg/dL [1.7 mmol/L]) can then lead to loss of consciousness or even a seizure [36,37,39].

3.6.1.2. Diabetes Ketoacidosis

This acute complication of diabetes mellitus may be the first manifestation of previously undiagnosed type 1 diabetes or may result from increased insulin requirements in type 1 diabetes patients during the course of infection, trauma, myocardial infarction, or surgery. Poor compliance, either for psychological reasons or because of inadequate patient education, is probably the most common cause of recurrent diabetic ketoacidosis.

Patients with type 2 diabetes may also develop ketoacidosis under severe stress such as sepsis, trauma, or major surgery.

Pathogenesis: Acute insulin deficiency results in rapid mobilization of energy from stores in muscle and fat depots, leading to an increased flux of amino acids to the liver for conversion to glucose and of fatty acids for conversion to ketones (acetoacetate, β-hydroxybutyrate, and acetone). In response to both the acute insulin deficiency and the metabolic stress of ketosis, the levels of insulin-antagonistic hormones (corticosteroids, catecholamines, glucagon, and GH) are consistently elevated. Furthermore, in the absence of insulin, peripheral utilization of glucose and ketones is reduced. The combination of increased production and decreased utilization leads to an accumulation of these substances in blood, with plasma glucose levels reaching 500 mg/dL (27. 8 mmol/L) or more and plasma ketones reaching levels of 8-15 mmol/L or more. The hyperglycemia causes osmotic diuresis leading to depletion of intravascular volume. As this progresses, impaired renal blood flow reduces the kidney's ability to excrete glucose,

and hyperosmolality worsens. Severe hyperosmolality (>330 mOsm/kg) correlates closely with central nervous system depression and coma. The accumulation of ketones may cause vomiting, which exacerbates the intravascular volume depletion. In addition, prolonged acidosis can compromise cardiac output and reduce vascular tone. The result may be severe cardiovascular collapse with generation of lactic acid, which then adds to the already existent metabolic acidosis [36,37,40].

3.6.1.3. Hyperglycemic Hyperosmolar State:

This form of hyperglycemic coma is characterized by severe hyperglycemia, hyperosmolality, and dehydration in the absence of significant ketosis. Lethargy and confusion develop as serum osmolality exceeds 300 mOsm/kg, and coma can occur if osmolality exceeds 330 mOsm/kg. Underlying renal insufficiency or congestive heart failure is common. A precipitating event such as pneumonia, cerebrovascular accident, myocardial infarction, burns, or recent operation can often be identified [36,37].

3.6.1.4. Lactic Acidosis

It occurs in severely ill diabetic patients present with profound acidosis and but relatively low or undetectable levels of keto acids in plasma, with the presence of excessive plasma lactate (> 5 mmol/L). Lactic acid is the end product of the anaerobic metabolism of glucose. The chief pathway for removal of lactic acid is by hepatic (and to some degree renal) uptake for conversion first to pyruvate and eventually back to glucose, a process that requires oxygen. Lactic acidosis occurs when excess lactic acid accumulates in the blood. This can be the result of overproduction (tissue hypoxia). *Type A lactic acidosis* is associated with tissue hypoxia from hypovolemia or endotoxic shock and need not be associated with hyperglycemia. *Type B lactic acidosis* is defined as that which occurs in the absence of clinical evidence for tissue hypoxia and is associated with diabetes per se or with *biguanide therapy (Metformin)* [36,37].

3.6.2. Chronic DM complications:

3.6.2.1. Microvascular Complications:

Disease of the smallest blood vessels, the capillary and the precapillary arterioles. Microvascular disease involving the retina leads to diabetic retinopathy [42], and disease involving the kidney causes diabetic

nephropathy which overtime could evolve to renal failure. Small vessel disease may also involve the heart, and cardiomegaly with heart failure has been described in diabetic patients with patent coronary arteries [36,37,41,44].

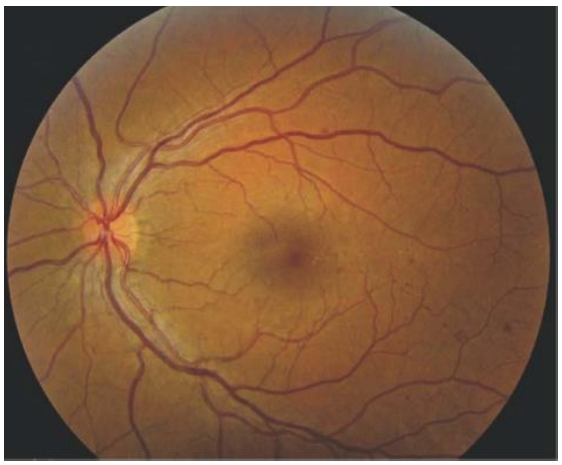


Figure 3.5. Non proliferative diabetic retinopathy with intraretinal hemorrhages and micro aneurysms along inferotemporal arcade; and hard exudates temporal to macula.

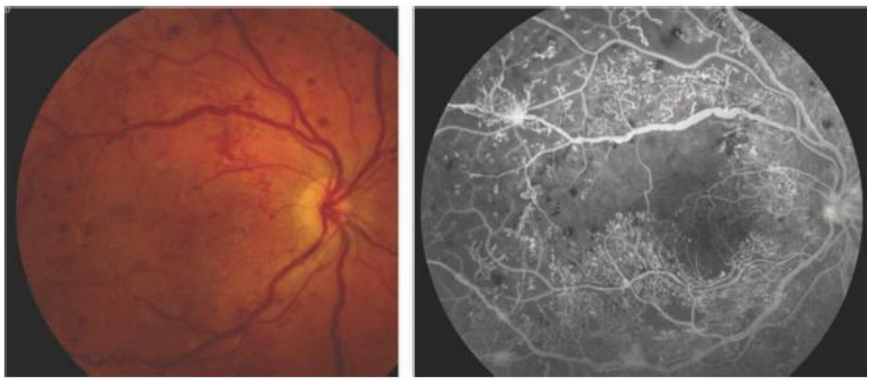


Figure 3.6. Proliferative diabetic retinopathy with neovascularization of the disc, venous beading, hemorrhages, and cotton wool spots nasal to the optic nerve. Early frame of fluorescein angiogram shows extensive macular capillary non perfusion and early leakage from neovascularization along the superotemporal arcade.

3.6.2.2. Macrovascular Complications:

Large vessel disease in diabetes is essentially an accelerated form of atherosclerosis. It accounts for the increased incidence of myocardial infarction, stroke, and peripheral gangrene in diabetic patients [36,37,43].

3.6.2.3. Neurologic complications (Diabetic Neuropathy):

Peripheral and autonomic neuropathies are the two most common complications of both types of diabetes. Up to 50% of patients with type 2 diabetes are affected [36,37,41].

- ***Peripheral Neuropathy:***
  A. **Distal symmetric polyneuropathy:** This is the most common form of diabetic peripheral neuropathy in which loss of function appears in a stocking-glove pattern and is due to an axonal neuropathic process. Longer nerves are especially vulnerable hence the impact on the foot. Both motor and sensory nerve conduction is delayed in the peripheral nerves [42].

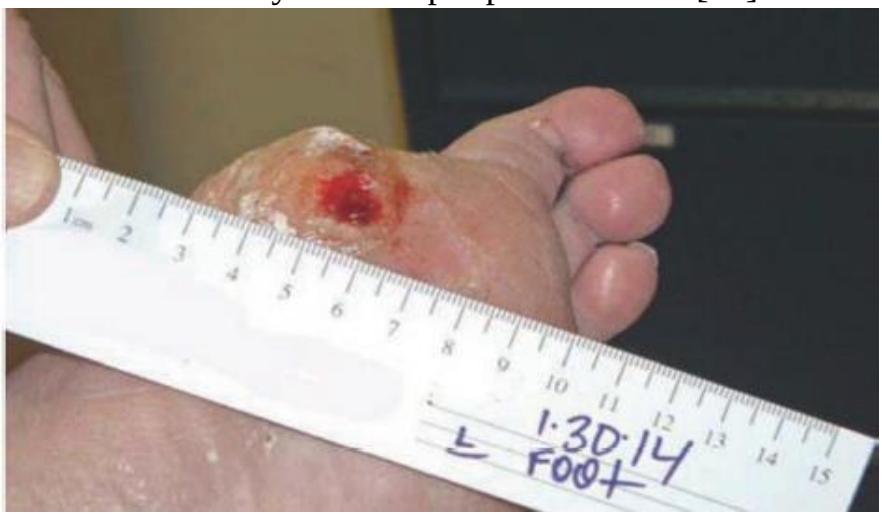


Figure 3.7 Neuropathic ulceration over first metatarsal head.

  B. **Isolated peripheral neuropathy:** Involvement of the distribution of only one nerve (mononeuropathy) or of several nerves (mononeuropathy multiplex) is characterized by sudden onset with subsequent recovery of all or most of the function. Cranial and femoral nerves are commonly involved, and motor abnormalities predominate.

- **Autonomic Neuropathy**
  Neuropathy of the autonomic nervous system is common in patients with diabetes of long duration. It can affect many diverse visceral functions including blood pressure and pulse, gastrointestinal activity, bladder function, and erectile function.

3.7. Glycemic Targets:

- An A1C goal: for many non- pregnant adults of <7% (53 mmol/mol) without significant hypoglycemia is appropriate.
- If using CGM to assess glycemia, an appropriate goal for many non-pregnant adults is time in range (TIR) of >70% with time below range

(TBR) <4% and time <54 mg/dL <1%. For those with frailty or at high risk of hypoglycemia, a target of >50% time in range with <1% time below range is recommended.

- Less stringent A1C goals (such as <8%[64mmol/mol]) may be appropriate for patients with limited life expectancy or where the harms of treatment are greater than the benefits.
- Occurrence and risk for hypoglycemia should be reviewed at every encounter and investigated as indicated [39].

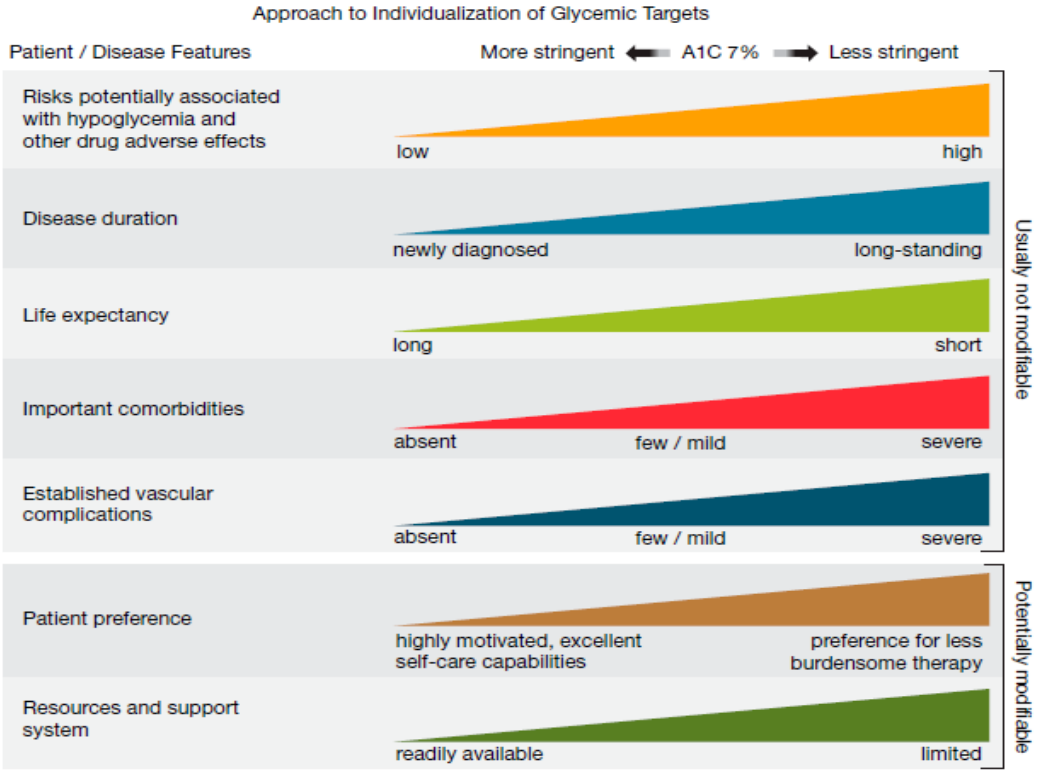


Figure 3.8. Patient and disease factors used to determine optimal glycemic targets. Characteristics and predicaments toward the left justify more stringent efforts to lower A1C; those toward the right suggest less stringent efforts. A1C:7%=53mmol/mol.

Glycemic recommendations for non-pregnant adults with diabetes	
A1c	<7.0% (53mmol/mol)
Pre-prandial capillary plasma glucose	80-130 mg/dl
Peak postprandial capillary plasma glucose	<180 mg/dl

Table 3.5. Summary of Glycemic recommendations for non-pregnant adults with diabetes.

3.8. Diabetes Technology:

3.8.1. Blood glucose self-monitoring:

Capillary blood glucose measurements performed by patients themselves, are extremely useful. Optimal use of BGM devices requires proper review and interpretation of data by both the person with diabetes and the healthcare professional to ensure that data are used in an effective and timely manner. In people with type 1 diabetes, there is a correlation between greater BGM frequency and lower A1C. People with diabetes should be taught how to use BGM data to adjust food intake, physical activity, or pharmacologic therapy to achieve specific goals [45].

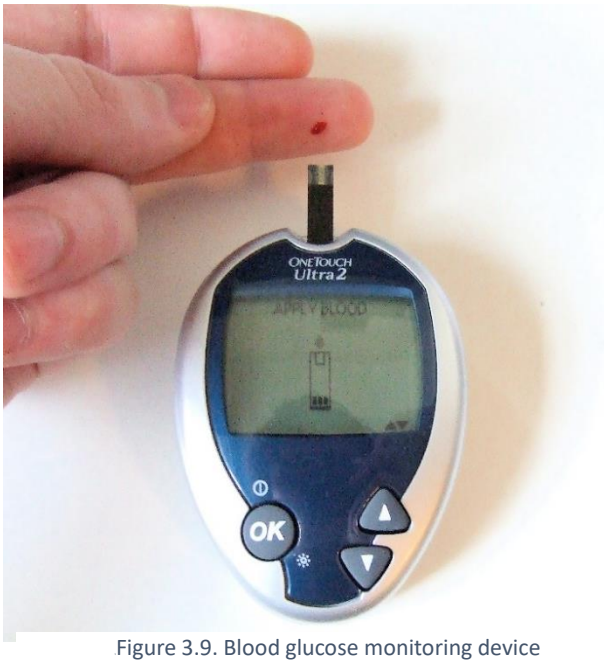
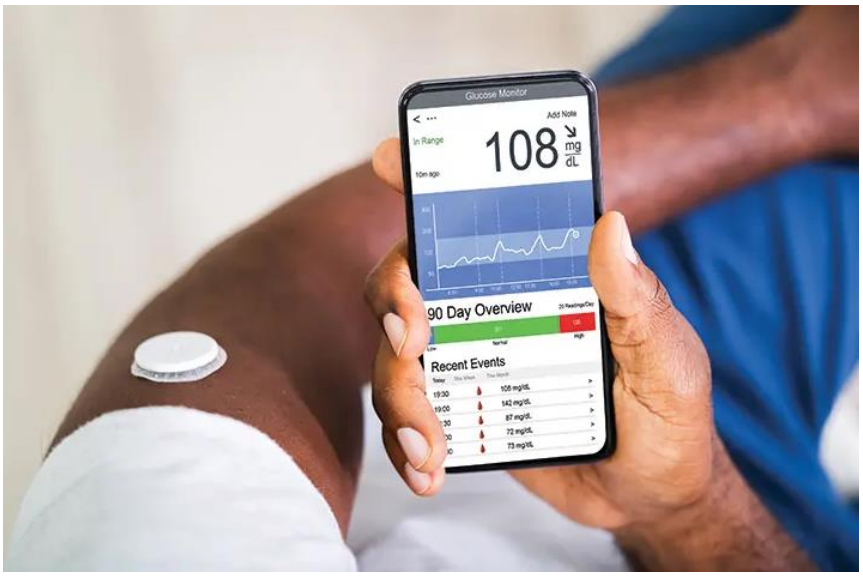


Figure 3.9. Blood glucose monitoring device

3.8.2. Continuous glucose monitoring devices:

Real-time CGM is increasingly utilized for routine diabetes care in adults, children, and adolescents with T1DM. CGM is a portable device that allows for measuring and visualizing glucose concentrations in the interstitial fluid in real time for 3 to 14 days. The glucose values are available for review by the patient at time of measurement. CGM devices are composed of three main units: a sensor, a transmitter, and a receiver. The sensing electrode is placed in the subcutaneous space and measures glucose in the interstitial fluid, which is correlated to blood glucose via a calibration procedure. The sensing electrode is inserted by the user or a caregiver for most devices or implanted by a clinical team for the new long-term sensor. Each sensor can last between 3 and 14 days for the minimally invasive CGMs, and from 90 to 180 days for the implantable one. Information from the sensing electrode is transmitted to a dedicated receiver or to a smart device like a phone or an insulin pump. The dedicated receiver, an app on a smart phone or an insulin pump, receives the glucose readings, which then can be used to visualize glucose trajectories and provide hypoglycemia and hyperglycemia alerts and alarms to the user and followers.

Benefits of CGM devices have accrued with improved performance of the devices over time. Consistent CGM use of 6 or more days per week has been associated with improvements in glycemic control, reflected in lower HbA1c levels, more patients achieving HbA1c targets, and reduction in time in the hypoglycemic range of less than 70 mg/dL (<3.9 mmol/L) or less than 54 mg/dL (3 mmol/L) [45].



The CGM devices offer several metrics for healthcare providers in order to better evaluate the patient glycemic control and further improve treatment plan [45].

Figure 3.10. CGM sensor and reading app.

—Standardized CGM metrics for clinical care in nonpregnant individuals with type 1 or type 2 diabetes

Metric	Interpretation	Goals
1. Number of days CGM device is worn		14-day wear for pattern management
2. Percentage of time CGM device is active		70% of data from 14 days
3. Mean glucose	Simple average of glucose values	*
4. Glucose management indicator	Calculated value approximating A1C (not always equivalent)	*
5. Glycemic variability (%CV) target	Spread of glucose values	≤36%†
6. TAR: % of readings and time >250 mg/dL (>13.9 mmol/L)	Level 2 hyperglycemia	<5% (most adults); <10% (older adults)
7. TAR: % of readings and time 181–250 mg/dL (10.1–13.9 mmol/L)	Level 1 hyperglycemia	<25% (most adults); <50% (older adults)‡
8. TIR: % of readings and time 70–180 mg/dL (3.9–10.0 mmol/L)	In range	>70% (most adults); >50% (older adults)
9. TBR: % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L)	Level 1 hypoglycemia	<4% (most adults); <1% (older adults)§
10. TBR: % of readings and time <54 mg/dL (<3.0 mmol/L)	Level 2 hypoglycemia	<1%

CGM, continuous glucose monitoring; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range. *Goals for these values are not standardized. †Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycemia for those receiving insulin or sulfonylureas. ‡Goals are for level 1 and level 2 hyperglycemia combined. §Goals are for level 1 and level 2 hypoglycemia combined. Adapted from Battelino et al. (32).

Table 3.6. Standardized CGM metrics for clinical care.

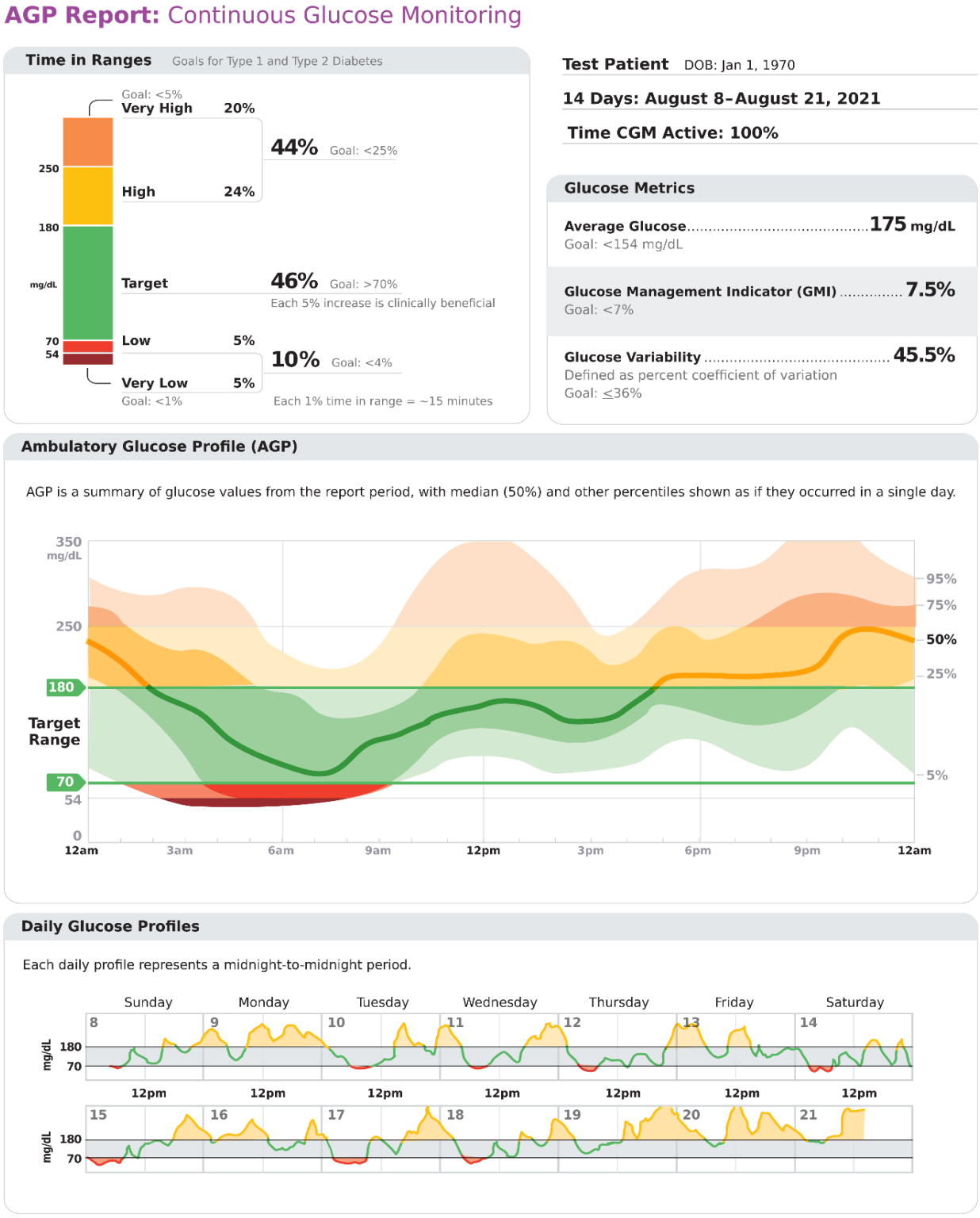


Figure 3.11. Key points included in standard ambulatory glucose profile (AGP) report.

Substances and Factors Affecting Continuous Glucose Monitoring Accuracy: Sensor interference due to several medications/substances is a known potential source of CGM measurement errors.

—Continuous glucose monitoring devices interfering substances

Medication	Systems affected	Effect
Acetaminophen		
>4 g/day	Dexcom G6, Dexcom G7	Higher sensor readings than actual glucose
Any dose	Medtronic Guardian	Higher sensor readings than actual glucose
Ascorbic acid (vitamin C), >500 mg/day	FreeStyle Libre 14 day, FreeStyle Libre 2, FreeStyle Libre 3	Higher sensor readings than actual glucose
Hydroxyurea	Dexcom G6, Dexcom G7, Medtronic Guardian	Higher sensor readings than actual glucose
Mannitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose
Sorbitol (intravenously or as peritoneal dialysis solution)	Senseonics Eversense	Higher sensor readings than actual glucose

Table 3.7. CGM interfering substances.

3.8.3. Insulin Pumps and Automated Insulin Delivery Systems:

Continuous Subcutaneous Insulin Infusion--CSII is a minimally invasive form of insulin delivery that enables intensive insulin therapy. One of the advantages of the use of CSII, is its ability to continuously deliver insulin and allow the users to respond more rapidly to any changes in their physiologic insulin requirements. Second, most modern CSII pumps enable the user to program and modify key parameters that effect insulin delivery, such as (1) *the basal rate profile*, in which several basal rates with multiple insulin segments can be entered to address changes in insulin requirements between workdays and weekends, active days or sick days, and more; (2) the storing of *multiple sensitivity factors*, as well as carbohydrate to insulin ratio; (3) *alerts and alarms*; (4) *bolus calculators* and insulin-on-board estimators, to prevent over-stacking of insulin.

CSII therapy has been associated with improved glycemic control, decreased hypoglycemia, and better quality of life. Still, there are several disadvantages of this delivery route. Using CSII means that the user is attached to an external device, which may be inconvenient in daily life. Additionally, it is recommended to change the infusion set every 3 days to reduce problems with site irritation and irregularity in insulin delivery caused by blocked catheters, insulin leakage, or cannula dislodgement. A failure of the infusion site can lead to hyperglycemia, and potentially DKA [36,37,45].

3.8.4. AID: "The Artificial Pancreas"

The combination of continuous glucose technology with insulin pumps has enabled the development of AID systems (closed loop or artificial pancreas devices). A controller, an algorithm, adjusts insulin delivery based on CGM data to a glucose target or range that is preset and can be changed based on user lifestyle or need. These feedback control algorithms achieve safe and effective glucose regulation for people with T1DM, maximize time spent within the euglycemic safe range of 70 to 180 mg/dL, minimize hypoglycemic events, and prevent postprandial hyperglycemia with little user intervention.

A closed-loop glucose control or AID system is composed of several basic elements, as depicted in Figure 3.13. The source of information is the sensor module that is based on a CGM. The delivery module is based on an insulin pump. The core module, the control algorithm, processes the sensor measurements with or without additional input provided by the user, such as meal or exercise information, to achieve the desired glucose set-point target or range. The control signal is sent to the user's pump to manipulate insulin delivery and other drugs, such as glucagon, in a variable rate or micro-dose. Current artificial pancreas systems are based on subcutaneous sensing and delivery [36,37,45].

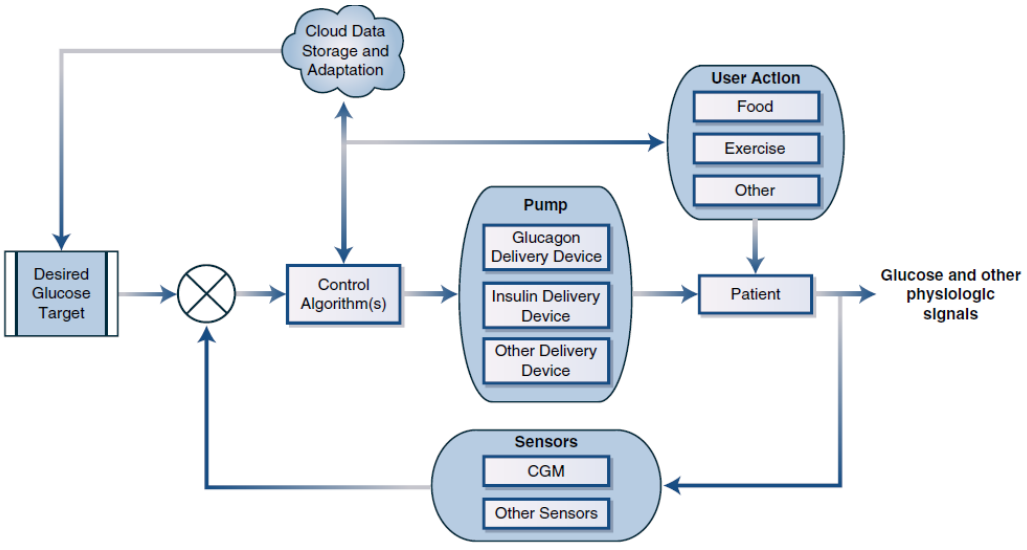


Figure 3.12. Feedback control loop for automated glucose management. CGM, continuous glucose monitoring.

Chapter 4: Theoretical background on deep learning

4.1. Fundamentals of Deep learning:

Deep learning is a machine learning method which has seen a rise the last years due to its ability to perform predictions on huge amounts of complex data using varied type and sizes of models [46]. One of the most common characteristics of these models is their large number of hidden neurons. These neurons may vary in how they receive and send out data, but the fundamental basic neuron is the artificial neuron. Artificial neurons are the basic structure of all deep learning networks and was created in a way to mimic the human neural neuron. The artificial neuron works in such a way that it receives input data that is weighted and added together with a bias, and finally a non-linear activation function is used which results in the output of the neuron [46]. These neurons can then be added together in a layer called a hidden layer, in a way that each neuron takes in all parts of the input data to that layer. By adjusting weights and biases, the network can train and learn from the data it is fed. Afterwards, a testing phase where the network is fed with unseen data is required.

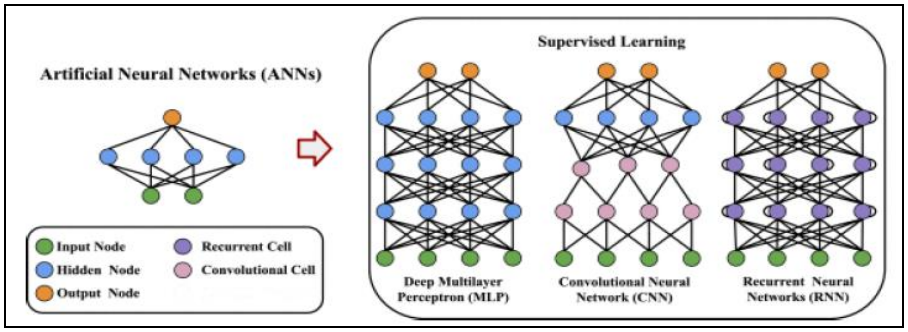


Figure 4.1. The different kinds of deep neural networks, with the artificial neural network to the left and the three most common types of supervised learning networks in the middle (MLP, CNN and RNN). © 2020 IEEE.

4.2. Learning methods in deep learning

4.2.1. Supervised learning

Supervised learning is all about operating to a known expectation and in this case, what needs to be analyzed from the data being defined. Algorithms classified under this category focus on establishing a relationship between

the input and output attributes, and use this relationship speculatively to generate an output for new input data points [48].

4.2.2. Unsupervised learning

In some of the learning problems, we do not have any specific target in mind to solve. The goal in this case is to decipher the structure in the data against the build mapping between input and output attributes of data and, in fact, the output attributes are not defined [48].

4.2.3. Semi-supervised learning

This learning technique is the combination of supervised and unsupervised learning. Semi-supervised learning is about using both labeled and unlabeled data to learn models better. Semi-supervised learning gets its motivation from the human way of learning [48].

4.2.4. Reinforcement learning

Reinforcement learning is learning that focuses on maximizing the rewards from the result. It involves interacting with the surrounding environment. The most important thing is that in reinforcement learning the model is additionally responsible for making decisions for which a periodic reward is received. The results in this case, unlike supervised learning, are not immediate and may require a sequence of steps to be executed before the final result is seen. Ideally, the algorithm will generate a sequence of decisions that helps achieve the highest reward or utility [48]. The goal in this learning technique is to measure the trade-offs effectively by exploring and exploiting the data [70].

Model	Unsupervised	Supervised	Software
Autoencoder	✓		Keras (Chollet, 2015), R: dimRed (Kraemer et al., 2018), h2o (Candel et al., 2015), RcppDL (Kou and Sugomori, 2014)
Convolutional Deep Belief Network (CDBN)	✓	✓	R & python: TensorFlow (Abadi et al., 2016), Keras (Chollet, 2015), h2o (Candel et al., 2015)
Convolutional Neural Network (CNN)	✓	✓	R & python: Keras (Chollet, 2015) MXNet (Chen et al., 2015), Tensorflow (Abadi et al., 2016), h2O (Candel et al., 2015), fastai (python) (Howard and Gugger, 2018)
Deep Belief Network (DBN)	✓	✓	RcppDL (R) (Kou and Sugomori, 2014), python: Caffee (Jia et al., 2014), Theano (Theano Development Team, 2016), Pytorch (Paszke et al., 2017), R & python: TensorFlow (Abadi et al., 2016), h2O (Candel et al., 2015)
Deep Boltzmann Machine (DBM)		✓	python: boltzmann-machines (Bondarenko, 2017), pydbm (Chimera, 2019)
Denoising Autoencoder (dA)	✓		Tensorflow (R, python) (Abadi et al., 2016), Keras (R, python) (Chollet, 2015), RcppDL (R) (Kou and Sugomori, 2014)
Long short-term memory (LSTM)		✓	rnn (R) (Quast, 2016), OSTSC (R) (Dixon et al., 2017), Keras (R and python) (Chollet, 2015), Lasagne (python) (Dieleman et al., 2015), BigDL (python) (Dai et al., 2018), Caffe (python) (Jia et al., 2014)
Multilayer Perceptron (MLP)		✓	SparkR (R) (Venkataraman et al., 2016), RSNNS (R) (Bergmeir and Benitez, 2012), keras (R and python) (Chollet, 2015), sklearn (python) (Pedregosa et al., 2011), tensorflow (R and python) (Abadi et al., 2016)
Recurrent Neural Network (RNN)		✓	RSNNS (R) (Bergmeir and Benitez, 2012), rnn (R) (Quast, 2016), keras (R and python) (Chollet, 2015)
Restricted Boltzmann Machine (RBM)	✓	✓	RcppDL (R) (Kou and Sugomori, 2014), deepnet (R) (Rong, 2014), pydbm (python) (Chimera, 2019), sklearn (python) (Chimera, 2019), Pylearn2 (Goodfellow et al., 2013), TheanoLM (Enarvi and Kurimo, 2016)

Table 4.1. List of popular deep learning models, available learning algorithms (unsupervised, supervised) and software implementations in R or python.

4.3. Training on Deep Learning networks

When the network has been created the training can start. The way neural networks train is by adjusting the weights and biases by a pre-determined step size, referred to as learning rate, by the use of a cost or loss function.

By training the data goes through the network until it arrives to the final layer, where the loss function will compare the label to the network output, and which this result will be propagated back through the network, *back propagating*, and change each neuron's weights and biases with regards to the learning rate in how much they will be changed. The network will attempt to reduce the loss and increase the performance as much as it can, with the help of an optimizer. Each layer has activation functions, which can be in the form of sigmoid, tanh, ReLU or Leaky-ReLU. Also, the most common optimizer being Stochastic Gradient Descent (SGD), RMSprop and Adaptive Momentum Estimation (Adam) [47]. The data is usually divided into training, validation and test sets, with validation being tested on during training to adjust the network. The test data is tested on when all training is done to investigate how well the network performs on unseen data.

4.4. Deep Learning Networks

One of the most popular neural networks is the convolutional neural network (CNN). It has achieved state of-the-art performance in many areas and continues to perform well [46,55]. The basic structure and what makes CNN so widely used is the mathematical operation, convolution [47,56]. Another common neural network is the recurrent neural network (RNN) which has seen more use in time series data and sequences. RNN allows latent information to pass over to the next unit in the network [57]. The general structure of the RNN can be seen in (Figure 4.2). While the RNN might perform well on short time series data, for longer time series data the network may experience the gradient either exploding or vanishing during back propagation. This behavior is a result of how the network is chained together and the use of gradient-based optimizer, such as SGD, resulting in the gradient rapidly increasing or decreasing [57,58]. To try to mitigate this, the **LSTM network** was proposed [59]. It is now one of the most popular RNN variations being used [60,61,62]. It introduces three parts to assist in

computation for the memory cell *ct*, namely the so called forget gate *ft*, input gate *it* and output gate *ot*

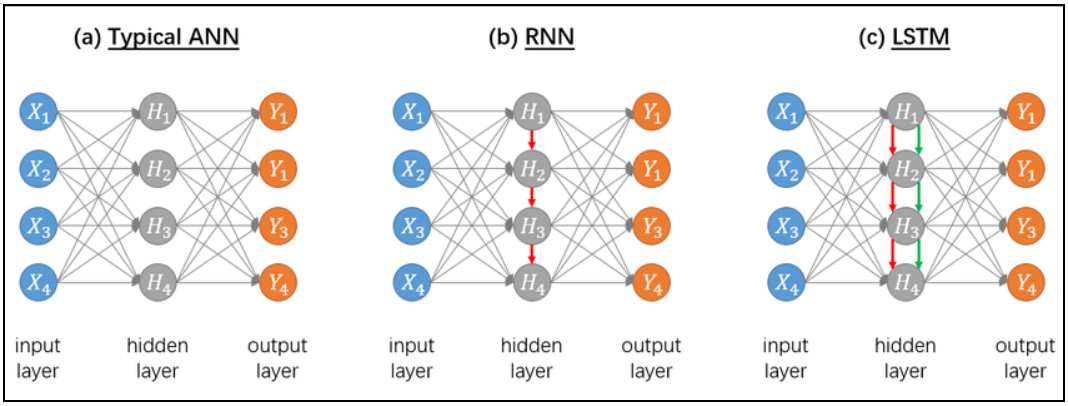


Figure 4.2 Structural differences between ANN, RNN an LSTM.

4.4.1 Recurrent Neural Networks and The Long Short-Term Memory Network (LSTM)

A recurrent neural network is a type of artificial neural network that is best suited to recognizing patterns in sequences of data, such as text, video, speech, language, genomes, and time-series data. the most effective sequence models used in practical applications are called **gated RNNs**. Like the LSTM.

The Concept of LSTM: Long short-term memory is a modified RNN architecture that tackles the problem of vanishing and exploding gradients and addresses the problem of training over long sequences and retaining memory. All RNNs have feedback loops in the recurrent layer. The feedback loops help keep information in "memory" over time. Since the gradient of the loss function decays exponentially with time (a phenomenon known as the vanishing gradient problem), it is difficult to train typical RNNs. That is why an RNN is modified in a way that it includes a memory cell that can maintain information in memory for long periods of time. In LSTM, a set of gates is used to control when information enters memory, which solves the vanishing or exploding gradient problem [51].

The idea of introducing self-loops to produce paths where the gradient can flow for long durations is a core contribution of the initial long short-term memory (LSTM) model (Hochreiter and Schmidhuber, 1997). A crucial addition has been to make the weight on this self-loop conditioned on the

context, rather than fixed (Gers et al., 2000). By making the weight of this self-loop gated, the time scale of integration can be changed dynamically [49].

The LSTM block diagram is illustrated in figure 4.3. The corresponding forward propagation equations are given below. Instead of a unit that simply applies an element wise nonlinearity to the affine transformation of inputs and recurrent units, LSTM recurrent networks have "LSTM cells" that have an internal recurrence (a self-loop), in addition to the outer recurrence of the RNN. Each cell has the same inputs and outputs as an ordinary recurrent network, but has more parameters and a system of gating units that controls the flow of information. The most important component is the state unit $s_i^{(t)}$ that has a linear self-loop similar to the leaky units described in the previous section. However, here, the self-loop weight (or the associated time constant) is controlled by a forget gate unit $f_i^{(t)}$ (for time step t and cell i), that sets this weight to a value between 0 and 1 via a sigmoid unit:

$$f_i^{(t)} = \sigma\left(b_i^f + \sum_j U_{ij}^f x_j^{(t)} + \sum_j W_{ij}^f h_j^{(t-1)}\right),$$

where $x^{(t)}$ is the current input vector and $h^{(t)}$ is the current hidden layer vector, containing the outputs of all the LSTM cells, and b^f, U^f, W^f are respectively biases, input weights and recurrent weights for the forget gates. The LSTM cell internal state is thus updated as follows, but with a conditional self-loop weight $f_i^{(t)}$:

$$s_i^{(t)} = f_i^{(t)} s_i^{(t-1)} + g_i^{(t)} \sigma\left(b_i + \sum_j U_{ij} x_j^{(t)} + \sum_j W_{ij} h_j^{(t-1)}\right),$$

where $\boldsymbol{b}$, $\boldsymbol{U}$ and $\boldsymbol{W}$ respectively denote the biases, input weights and recurrent weights into the LSTM cell. The external input gate unit $g_i^{(t)}$ is computed similarly to the forget gate (with a sigmoid unit to obtain a gating value between 0 and 1), but with its own parameters:

$$g_i^{(t)} = \sigma\left(b_i^g + \sum_j U_{ij}^g x_j^{(t)} + \sum_j W_{ij}^g h_j^{(t-1)}\right),$$

The output $h_i^{(t)}$ of the LSTM cell can also be shut off, via the output gate $q_i^{(t)}$, which also uses a sigmoid unit for gating:

$$h_i^{(t)} = \tan\left(s_i^{(t)}\right) q_i^{(t)},$$

$$q_i^{(t)} = \sigma\left(b_i^o + \sum_j U_{ij}^o x_j^{(t)} + \sum_j W_{ij}^o h_j^{(t-1)}\right),$$

which has parameters $\boldsymbol{b^o}$, $\boldsymbol{U^o}$, $\boldsymbol{W^o}$ for its biases, input weights and recurrent weights, respectively. Among the variants, one can choose to use the cell state $s_i^{(t)}$ as an extra input (with its weight) into the three gates of the i-th unit, as shown in figure 4.3. This would require three additional parameters [49].

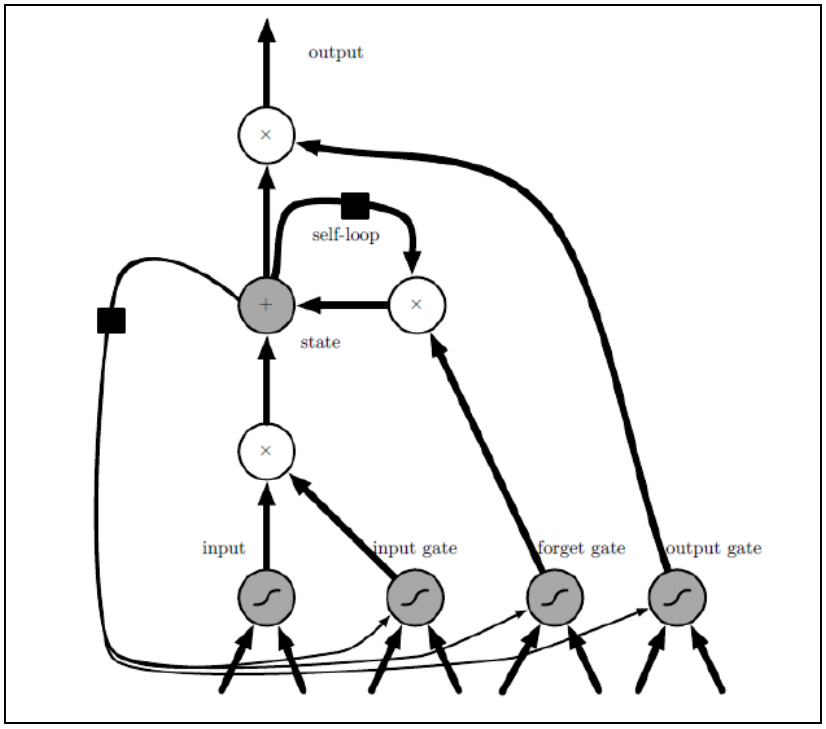


Figure 4.3. Block diagram of the LSTM recurrent network "cell." Cells are connected recurrently to each other, replacing the usual hidden units of ordinary recurrent networks. An input feature is computed with a regular artificial neuron unit. Its value can be accumulated into the state if the sigmoidal input gate allows it. The state unit has a linear self-loop whose weight is controlled by the forget gate. The output of the cell can be shut off by the output gate. All the gating units have a sigmoid nonlinearity, while the input unit can have any squashing nonlinearity. The state unit can also be used as an extra input to the gating units. The black square indicates a delay of a single time step.

4.5. Deep learning on time series data

Several different deep learning networks has been investigated on different types of time series data. Lynn et al. investigated the use of bi-directional LSTM and GRU networks on heartbeat detection of ECG data [63]. The results showed improvements of higher accuracy compared to using regular LSTM or GRU. Bi-directional LSTM and GRU networks were also investigated in ciphertext classification. Ahmadzadeh et al. tested using these networks and compared to a 1D CNN network and regular LSTM and GRU networks [60]. Both bi-directional networks performed better, with an increase of accuracy of around 1-2% depending on cypher.

Others have investigated networks combining RNN and CNN to extract both feature extraction from CNN and the time-dependency feature from RNN. Garcia et al compared proposed LSTM, CNN and LSTM-CNN networks where instead of working on 1D-CNN on power quality disturbances data, Garcia et al used a short time Fourier transform to get an image of each sequence consisting of spectral components and amplitudes to use as a seven-variable input [55]. The proposed CNN and LSTM-CNN networks performed very similar with small improved results while using the combined LSTM/CNN network, while the LSTM network performed much worse. Karim et al. investigated another such combined network, comparing with adding an attention layer achieving state-of-the-art results on several UCR benchmark datasets [65]. Another configuration of this network was tested by switching the LSTM to a GRU layer which showed improved training speed and even better results [64].

4.6. Blood Glucose Prediction

Deep learning in the diabetes field has mostly been focused on blood glucose prediction and to aid the closed and semi-closed systems to announce incoming hyper/hypo events and in a few to detect meals. Most networks also use additional variables than only blood glucose, such as basal and bolus insulin, to aid the network. One such study was done by Maxime De Bois et al [32]. the study used an LSTM based RNN and comparing it to other state-of-the-art models (Extreme Learning Machine, Gaussian Process regressor, Support Vector Regressor). The study shows that the proposed approach, outperforms all baseline results. More precisely, it trades a loss of 4.3% in the prediction accuracy for an improvement of the clinical acceptability of 27.1%. another study conducted by Eleonora Maria Aiello et al [33] used Deep Glucose Forecasting which is a method based on two-headed LSTM implementation. The model used in this method is based on stacked LSTM cells which are able to learn how to filter part of their hidden state during the inference process in order to model long-term temporal dependencies. The study achieved an error rate (RMSE: 27.29) that drops to (RMSE: 21.09) after fine tuning. A different study done by Yixiang Deng et al [34] that utilized the use of CNN, RNN (LSTM in particular) in addition to mixup (beyond empirical risk Minimization) and time-series generative adversarial networks (TimeGAN) and later suggested their best model (CNN+Transfer2) outperforms all other models in terms of mean absolute

error (MAE). The applied model achieved an Accuracy of 95.98%, sensitivity of 59.19% and specificity of 98.15%. Another BGM prediction model was applied by Toledo-Marín et al [31]. this study used the blood glucose risk score formula proposed by Kovatchev et al., models with different architectures were trained, including, RNN, GRU, LSTM network, and an encoder-like convolutional neural network (CNN). As a result of this study a (RMSE) of 16 mg/dL, 24 mg/dL, and 37 mg/dL were obtained for CNN prediction horizons of 15, 30, and 60 min, respectively.

4.7. Imbalanced data sets

Most biological and health data is often very imbalanced when viewing it on the basis of how often rare events occur [66]. A dangerous or unwanted event might occur rarely but might be vital to detect over regular events. This in turn makes training a neural network on such data more difficult and different techniques has been proposed to combat this issue of imbalanced data. To begin with, accuracy is not a good metric for evaluating a network which is being trained on an imbalanced training due to simply choosing the majority class would result in an accuracy of over 99%. Instead, metrics such as Receiver operating curve area under the curve (ROC-AUC), the harmonic mean between precision and recall (f1-score) and other metrics can be used to give a clearer view of how well the network performs on the classes [67].

The different techniques proposed to try to combat the imbalanced dataset problem is the following: with pre-processing techniques aiming to assist the network during the training phase, and algorithms such as threshold moving and ensembling for when evaluating on the test data [66]. Pre-processing techniques often refer to sampling, where sampling refers to three different ways to sample the data: oversampling, undersampling and hybrid sampling.

Oversampling is done by replicating samples of the minority class until a balanced dataset is achieved [68]. Undersampling instead tries to balance the dataset by either randomly or informatively remove samples from the majority class. Lastly, the hybrid sampling aims to combine both over- and undersampling, such as SMOTE which creates artificial samples out of the minority class [69]. There’s also cost-sensitive learning that uses different loss costs per class, penalizing the weights more if the minority class is mislabeled [66].

Chapter 5: Methods and Materials

5.1. Study Variables:

5.1.1. Study population:

A registry study on Diabetes Data Registry and Individualized Lifestyle Intervention (DiaDRIL) was initiated in Shanghai East Hospital and Shanghai Fourth People's Hospital affiliated to Tongji University since 2019.

In this study, the patients were recruited from DiaDRIL in Shanghai East Hospital (September 2019 to March 2021) and Shanghai Fourth Peopleś Hospital (June 2021 to November 2021), respectively [30].

The inclusion criteria were as follows: patients with diagnosed diabetes according to the 1999 World Health Organization (WHO) criteria; more than 18 years of age, willing to sign the informed consent form and with CGM recording for at least 3 days.

Patients were excluded if they reported alcohol or drug abuse, were unable to comply with the study, or were not suitable to attend this study judged by the investigators. Data was anonymous to protect the sensitive information of the patients.

5.1.2. Data records:

The datasets ShanghaiT1DM and ShanghaiT2DM comprise two folders named "Shanghai_T1DM" and "Shanghai_T2DM" and two summary sheets named "Shanghai_T1DM_Summary" and "Shanghai_T2DM_Summary"

The "Shanghai_T1DM" folder and "Shanghai_T2DM" folder contain 3 to 14 days of CGM data corresponding to 12 patients with T1DM and 100 patients with T2DM, respectively. Of note, for one patient, there might be multiple periods of CGM recordings due to different visits to the hospital, which were stored in different excel tables. In fact, collecting data from different periods in one patient can reflect the changes of diabetes status during the follow-up. The excel table is named by the patient ID, period number and the start date of the CGM recording. Thus, for 12 patients with T1DM, there are 8 patients with 1 period of the CGM recording and 2 patients with 3 periods, totally equal to 16 excel tables in the

"Shanghai_T1DM" folder. As for 100 patients with T2DM, there are 94 patients with 1 period of CGM recording, 6 patients with 2 periods, and 1 patient with 3 periods, amounting to 109 excel tables in the "Shanghai_T2DM" folder. Overall, the excel tables include CGM BG values every 15 minutes or what equals to 96 values daily, capillary blood glucose (CBG) values, blood ketone, self-reported dietary intake, insulin doses and non-insulin hypoglycemic agents. The blood ketone was measured when diabetic ketoacidosis was suspected with a considerably high glucose level. Insulin administration includes continuous subcutaneous insulin infusion using insulin pump, multiple daily injections with insulin pen, and insulin that were given intravenously in case of an extremely high BG level.

5.1.3. Clinical attributes in the summary sheets:

The summary sheets summarize the clinical characteristics, laboratory measurements and medications of the patients included in this study.

- **Patient's gender:** Either male or female.
- **Age:** Age of the patient during the study.
- **Height:** Height of the patient.
- **Weight:** Weight of the patient.
- **BMI:** Body mass index of the patient.
- **Smoking history:** Clinical quantification of cigarette smoking used to measure a person's exposure to tobacco estimated by pack/year.
- **Alcohol drinking history:** Whether or not the patient drinks alcohol.
- **Type of DM:** Either T1DM or T2DM.
- **Duration of DM:** Duration of years since DM diagnosis.
- **Acute diabetic complication:** Whether or not the patient experienced diabetic ketoacidosis.
- **Diabetic Macrovascular Complications:** Including; coronary heart disease, peripheral arterial disease and cerebrovascular disease.
- **Diabetic Microvascular Complications:** Including; neuropathy, retinopathy, nephropathy.
- **Comorbidities:** The existence of other diseases that could complicate DM and increase mortality rate.

- **Hypoglycemic agents:** Whether the patient is on exogenous insulin or other oral hypoglycemic agents.
- **Other agents:** Mentions other drugs taken by patient which are not related to DM treatment.
- **Fasting plasma glucose (mg/dl):** Measurement of patient's glucose levels before food ingestion.
- **2-hour Postprandial Plasma Glucose (mg/dl):** Measurement of patient's glucose levels 2 hours after meal.
- **Fasting C-peptide (nmol/L):** Measurement of patient's c peptide before consuming food which is a substance that is created when the hormone insulin is produced and released into the body.
- **2-hour Postprandial C-peptide (nmol/L):** Measurement of patient's c-peptide 2 hours after meal.
- **Fasting Insulin (pmol/L):** Measurement of patient's insulin levels before food ingestion.
- **2-hour Postprandial insulin (pmol/L):** Measurement of patient's insulin levels 2 hours after meal.
- **HbA1c (mmol/mol):** Glycated hemoglobin is a form of hemoglobin that is chemically linked to a sugar. And it represents patients' glucose control over the previous 3 months period.
- **Glycated Albumin (%):** Reflects short-term glycemia over 1-3 weeks.
- **Total Cholesterol (mmol/L):** Measurement of patient's cholesterol levels.
- **Triglyceride (mmol/L):** Measurement of patient's Triglyceride levels.
- **High-Density Lipoprotein Cholesterol (mmol/L):**

Measurement of patient's HDL levels.

- **Low-Density Lipoprotein Cholesterol (mmol/L):**

Measurement of patient's LDL levels.

- **Creatinine (µmol/L):** Reflects patient's renal function.

- **Estimated Glomerular Filtration Rate (ml/min/1.73m2):** eGFR measures patient's level of kidney function and determines stage of kidney disease.
- **Uric Acid (mmol/L):** Measures patient's uric acid levels.
- **Blood Urea Nitrogen (mmol/L):** Measures the amount of urea nitrogen in the blood and reflects patient's kidney function.
- **Hypoglycemia (yes/no):** Whether the patient suffered hypoglycemia episodes.

5.1.4. CGM parameters:

Time in range (TIR), one of the critical CGM-derived metrics, reflects the glucose variability and evaluates the quality of glycemic control. It is associated with microvascular complications and macrovascular outcomes of diabetes. TIR is defined as the percentage of time spent in the target glucose range of 70–180 mg/dL. Time below range (TBR) and time above range (TAR) are the percentage of time when blood glucose is below 70 mg/dL and above 180 mg/dL, respectively.

5.2. Methodology

5.2.1. Data analysis

In this step we utilized "*Jupyter Notebook*" which is an open-source web application that allows you to create and share documents that contain live code, equations, visualizations, and narrative text. we worked to analyze the data using several python libraries (e.g., Pandas, NumPy, Seaborn, Matplotlib, Os).

To start with, we used the *seaborn* library to plot different variables from the patient's summary files from the data on both T1DM and T2DM patients. followed by using *NumPy* functions to perform statistical analysis on the data variables and later on we used the *Pandas* library to find correlations between the data variables then using both *seaborn* and *matplot* we visualized the heatmap to represent these correlations.

Then we calculated the time percentage for TAR, TBR and TIR for patients in both datasets as the higher values of TAR and TBR indicated that the patient's condition was more serious. Furthermore,

to give a clearer view of the TIR, TAR and TBR we calculated the mean ± standard deviation of these values for these two datasets.

Lastly, we plotted the CGM data for 3 patients and calculated the *Autocorrelation Function*, which represents the degree of similarity between a given time series and a lagged version of itself over successive time intervals. It can help to uncover hidden patterns in data.

$$\rho_k = \frac{E[(x_t - \mu)(x_{t-k} - \mu)]}{\sigma^2}$$

where x_t is the observation at time t, k is lag, E is the expected value operator, μ is the mean and σ^2 is the variance of the time series. ρ_k can show the correlation between two observations with a lag k in the time series.

5.2.2. The Neural Network Model

We worked with several python libraries on *"Jupyter Notebook"* (e.g., NumPy, Pandas, scipy, matplotlib, Sk-learn, TensorFlow, Keras).

First, The CGM data were mapped into risk score data by using the symmetrization formulas proposed by Kovatchev et al. [53,54],

$$y_t = \gamma(In^{\alpha}(x_t) - \beta),$$

where α = 1.084, β = 5.381, and ɣ = 1.509 are fitted parameters, x_t is the patient's glucose value and y_t is the BG risk variable. The BG risk score function is defined as $BG(yt) = 10 . y_t^2$.

The previous formula symmetrizes and rescales the glucose data such that $-\sqrt{10} \leq y_t \leq \sqrt{10}$.

Most activation functions in neural networks have a non-zero gradient in the interval [-1, 1] and, most importantly, zero gradients outside these bounds. For these reasons, the data is further transformed by dividing by $\sqrt{10}$ such that $\xi_t = y_t/\sqrt{10}$, where ξ_t shall be referred to as the blood glucose (BG) risk-standardized variable or standardized variable. The fact that the data are now bounded between -1 and 1 improves the model robustness. We used the MinMaxScaler from the SKlearn library to normalize the data, it transforms data such that all values are between 0 and 1. Then creating sequences from the data in order to run the model.

The work followed a methodology in which the data was divided into a training set comprising 70% of the total data, and a test set comprising 20% of the total data and a validation set comprising the remaining 10% of the total data.

By using a 70:20 ratio for the data split, a balance is achieved between having a sufficiently large training set for building strong models and a smaller test set that reflects the diversity and represents the overall data. This type of split helps objectively assesses model performance and provide an accurate estimation of their predictive ability on new data.

- ***The LSTM Neural Network Model Configuration:***

  The neural network model consists of two layers: an ***LSTM layer*** and a ***dense layer***. The **LSTM layer** is a type of recurrent neural network (RNN) that is well-suited for processing sequential data. The **dense layer** is a fully connected layer that takes the output of the LSTM layer and uses it to make predictions or classifications.

  In this specific model, the LSTM layer has 50 units, so that it can store 50 values in its memory cell at each time step. The dense layer has 1 unit, which means that it can make a single prediction. The model has a total of 10,451 trainable parameters. This includes the weights and biases of the LSTM layer and the dense layer.

```
# Define LSTM model
model = Sequential()
model.add(LSTM(50, activation='relu', input_shape=(n_steps_in, 1)))
model.add(Dense(1))
model.compile(optimizer='adam', loss='mse')
```

Figure 5.1. The LSTM python code.

The model uses the ReLU activation function. The model is compiled using the Adam optimizer and the mean squared error (MSE) loss function.

The ReLU activation function is a non-linear function that is defined as $f(x) = max(0,x)$. This means that the output of the LSTM layer will be a non-negative value. The linear activation function is a function that is defined as $f(x) = x$. This means that the output of the dense layer will be a linear function of the input.

The Adam optimizer is a stochastic gradient descent optimizer that is designed to be computationally efficient.

The MSE loss function is a measure of how different the predicted output of the model is from the actual output.

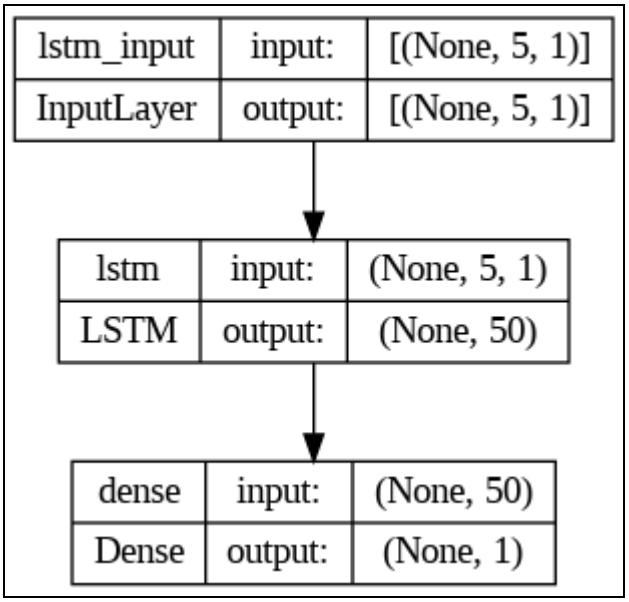


Figure 5.2. LSTM network structure.

After applying the model, we plotted the RMSE and the loss performance. And later choosing a patient to apply the model on and plotting the resulting predictions. And lastly using the Clarke error grid to assess the safety evaluation of the predictions.

NumPy	NumPy is a widely used python library, it stands for "Numerical python" and is the core library for scientific computing in Python. provides a multidimensional array object, various derived objects (such as masked arrays and matrices), and an assortment of routines for fast operations on arrays, including mathematical, logical, shape manipulation, sorting, selecting, I/O, discrete Fourier transforms, basic linear algebra, basic statistical operations, random simulation and much more.
Pandas	Pandas is a Python library for data manipulation and analysis. It provides a wide range of functions for data manipulation, including filtering, grouping, merging, reshaping, Iteration, Concatenation, Conversion of data, Visualizations, Aggregations and pivoting. It also provides tools for handling missing data, time-series data, and input/output operations.

SciPy	is a Python library for scientific computing that builds on top of NumPy. It provides a wide range of algorithms for optimization, integration, interpolation, eigenvalue problems, algebraic equations, differential equations, statistics, and many other classes of problems. It also provides specialized data structures, such as sparse matrices and k-dimensional trees.
Sk-learn (Scikit-learn)	Sklearn is a Python library for machine learning that provides simple and efficient tools for predictive data analysis. It offers various algorithms for classification, regression, clustering, dimensionality reduction, model selection, and preprocessing
Seaborn	is a Python data visualization library that is built on top of Matplotlib and integrates closely with Pandas data structures. It provides a high-level interface for creating various types of charts, such as histograms, boxplots, violin plots, and more. Seaborn is designed to work with complex datasets and can be used to create informative and attractive visualizations.
Matplotlib	Matplotlib is a Python library for creating static, animated, and interactive visualizations in Python. It provides a wide range of plot types, including line plots, scatter plots, bar plots, histograms, and more. It is widely used in scientific computing, data analysis, and machine learning.
TensorFlow	TensorFlow is a Python-friendly open-source library for numerical computation that makes machine learning and developing neural networks faster and more efficient. TensorFlow allows developers to create dataflow graphs, structures that describe how data moves through a graph or a series of processing nodes. Each node in the graph represents a mathematical operation, and each connection or edge between nodes is a multidimensional data array, or tensor.it is widely used in machine learning, deep learning, and artificial intelligence.
Keras	Keras is a Python library for deep learning that provides a user-friendly interface for building and training neural networks. Keras is built on top of TensorFlow and allows you to define and train neural network models in just a few lines of code. It provides a wide range of pre-built layers, activation functions, loss functions, and optimizers (e.g., Sequential, LSTM, Dense), making it easy to build and train complex models.

Table 5.1. Introduction to the python libraries used in this thesis.

Chapter 6: Results and Discussion

6.1. Data Analysis and Descriptive Statistics

6.1.1. Type 1 Diabetes Mellitus data (T1DM):

➢ **Descriptive Statistics:**

- **Age:**

The average age of patients with T1DM in the data is 59 with a standard deviation of 10.15 as shown in table 6.1.

	N	Min	Max	Mean	Standard deviation
Age (years)	16	37	73	59	10.15

Table 6.1. Average age of T1DM patients.

and the age distribution of patients' age is shown in the figure 6.1.

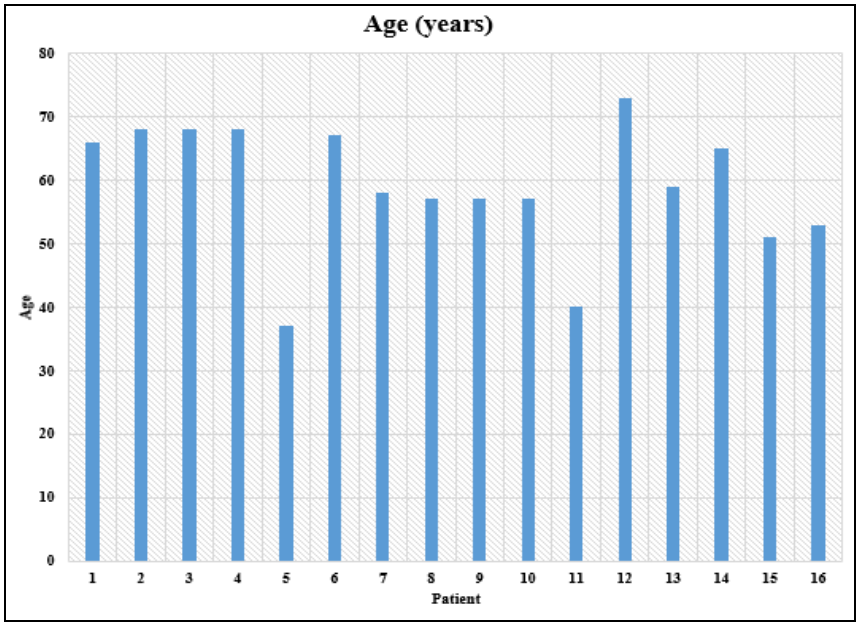


Figure 6.1. Age distribution in T1DM.

- **Fasting Plasma Glucose (mg/dl)**

In the data, the patient's fasting plasma glucose values range from 80.52 to 352.80 with a mean of 193.23 and a standard deviation of 86.49 as shown in table 6.2.

	N	Min	Max	Mean	Standard deviation
Fasting plasma glucose (mg/dl)	16	80.28	352.80	193.23	86.49

Table 6.2. statistics of patients' fasting plasma glucose.

The next figure (6.2) shows the range of fasting plasma glucose among patients. which is an important metric in evaluating each patient's condition and glycemic control thus adjusting their treatment plan as necessary if the values are not satisfactory.

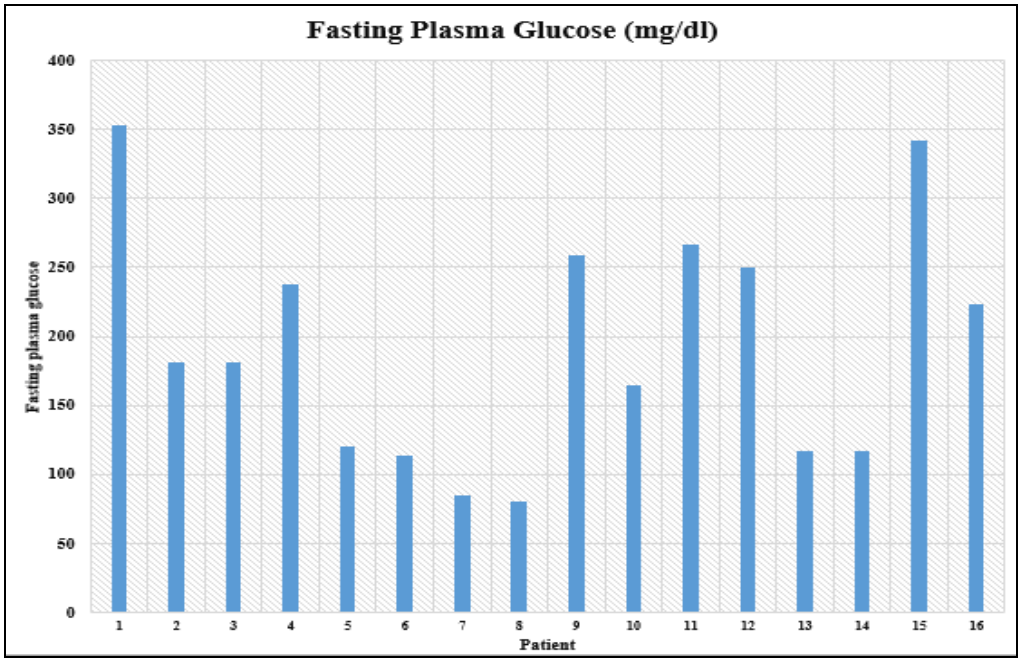


Figure 6.2. patients' fasting blood glucose.

- **2hr Postprandial plasma glucose:**

While fasting plasma glucose values are an important way to assess glycemic control. Physicians need to have an idea on the patient's glucose values after meals which provide an essential information on whether the patient is committed to the diabetes diet and their body's response to glucose load. As shown in table 6.3 and figure 6.3, patients' 2 hr postprandial glucose values range from 72.54 to 372.96 with a mean of 268.76 which gives an understanding that most of the patients in this study have poor glycemic control since as physicians we aim for a postprandial glucose value less than 180 mg/dl.

	N	Min	Max	Mean	Standard deviation
2-hr postprandial plasma glucose (mg/dl)	16	72.54	372.96	268.76	82.02

Table 6.3 statistics of patients' 2-hr postprandial plasma glucose.

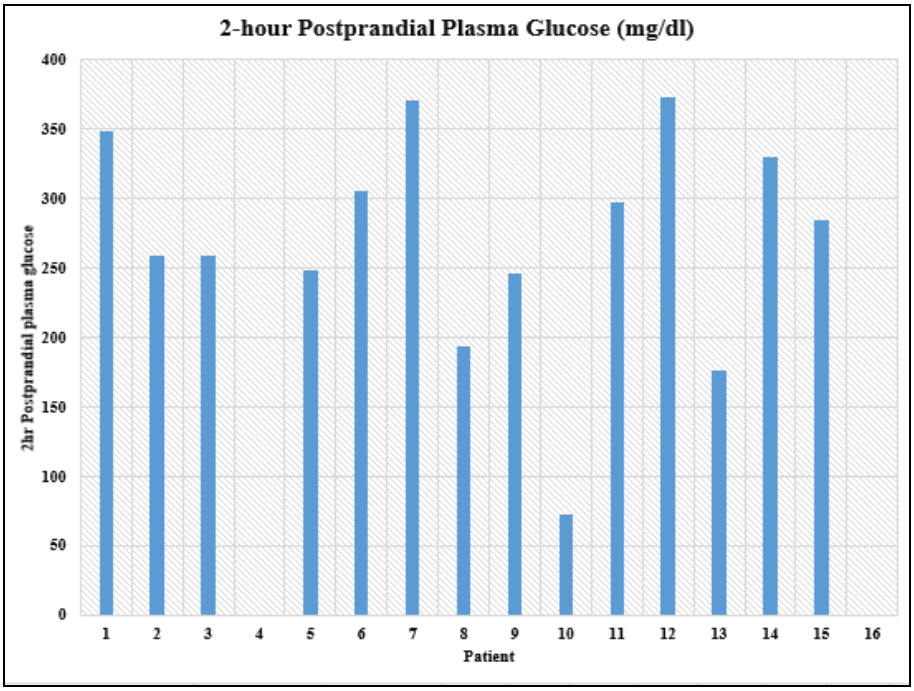


Figure 6.3 2-hr postprandial plasma glucose.

- **HbA1c:**

The Glycosylated hemoglobin is an important metric to evaluate the diabetic patient. It represents the patient's glycemic control over the previous 3 months period and it offers an immense help in deciding to adjust the treatment plan. in the available data the patients' HbA1c ranges from 54.10 to 165.59 as shown in table 6.4 and figure 6.4. in treatment goals the preferable value of HbA1c is less than 53 mmol/mol.

	N	Min	Max	Mean	Standard deviation
HbA1c (mmol/mol)	16	54.10	165.59	83.32	32.75

Table 6.4. HbA1c descriptive statistics.

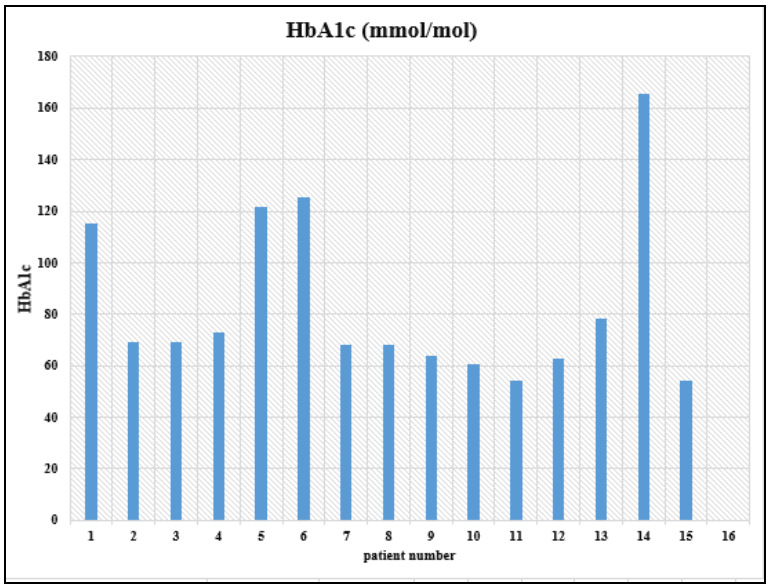


Figure 6.4. distribution of HbA1c in T1DM patients.

- **Acute Complications; Diabetic ketoacidosis and hypoglycemia**

The most important goal of treatment is to avoid acute complications of diabetes. These complications can have catastrophic effects of patient and may even lead to death in severe cases. The two main acute complications are diabetic ketoacidosis and hypoglycemia.

Diabetic Ketoacidosis: is an emergency that occurs mainly in T1DM patients. and is the result of extremely elevated glucose values. Figure 6.5. assess the occurrence of DKA in the employed data.

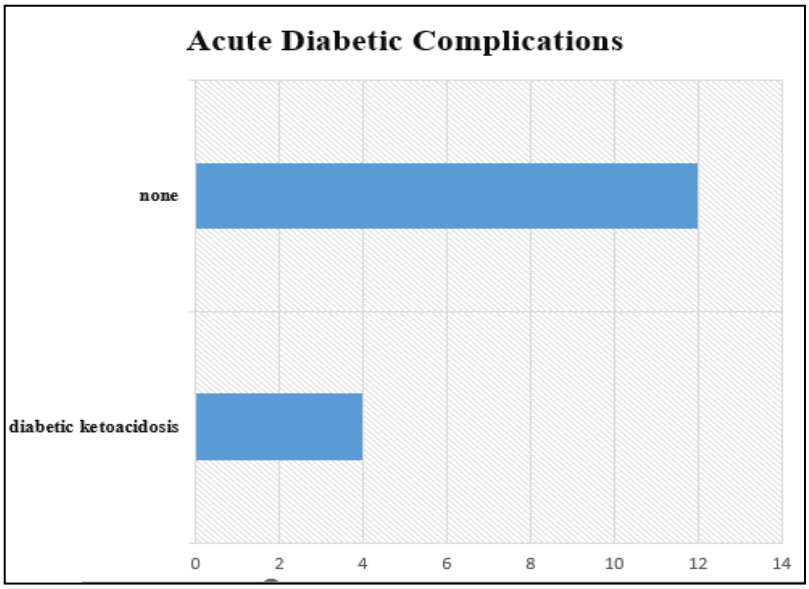


Figure 6.5. the occurrence of Diabetic ketoacidosis in T1DM patients.

Hypoglycemia: another acute complication of diabetes treatment and it's the results of low glucose values. All diabetic patient on insulin or other glucose lowering drugs are susceptible to hypoglycemia episodes. These episodes could be an important indicator to reassess the treatment and adjust as necessary. As shown in figure 6.6. out of the 16 patients in the dataset, 14 had hypoglycemic episodes while only 2 didn't have hypoglycemic episodes in the duration of the study.

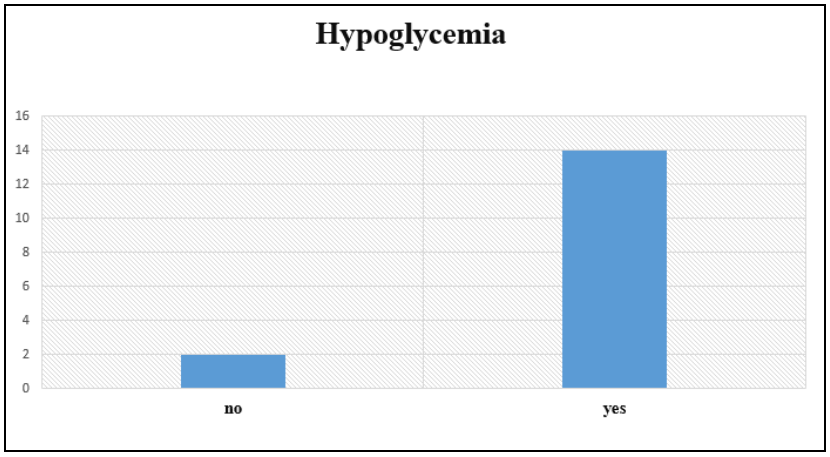


Figure 6.6. the incidence of hypoglycemic episode in T1DM patients.

- **Diabetic Macrovascular Complications:**

over the years, diabetic patients are susceptible to the chronic diabetic complications especially the ones with poor glycemic control. As shown in figure 6.7, The patients were assessed for macrovascular complications of diabetes which include; peripheral arterial disease, coronary heart disease and cerebrovascular disease.

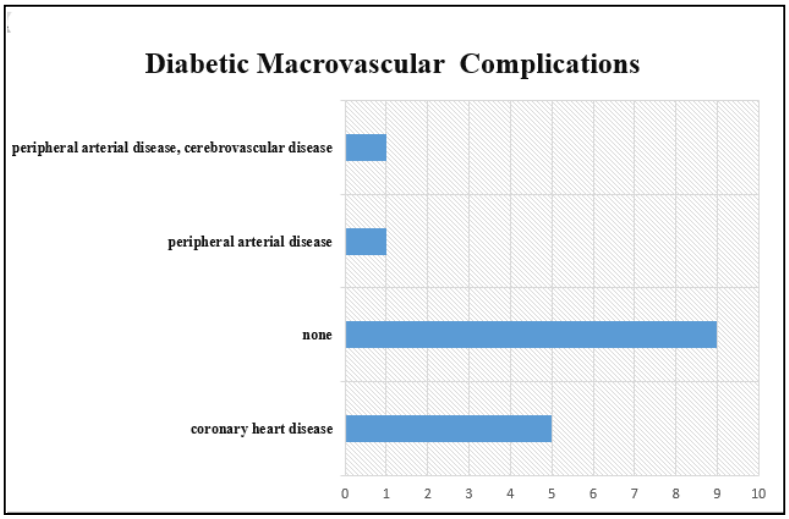


Figure 6.7. The occurrence of diabetic macrovascular complications in T1DM.

- **Diabetic Microvascular Complications**

The microvascular complications of diabetes include; Neuropathy, Nephropathy and Retinopathy. the following figure 6.8. shows the occurrence of these complications in T1DM data.

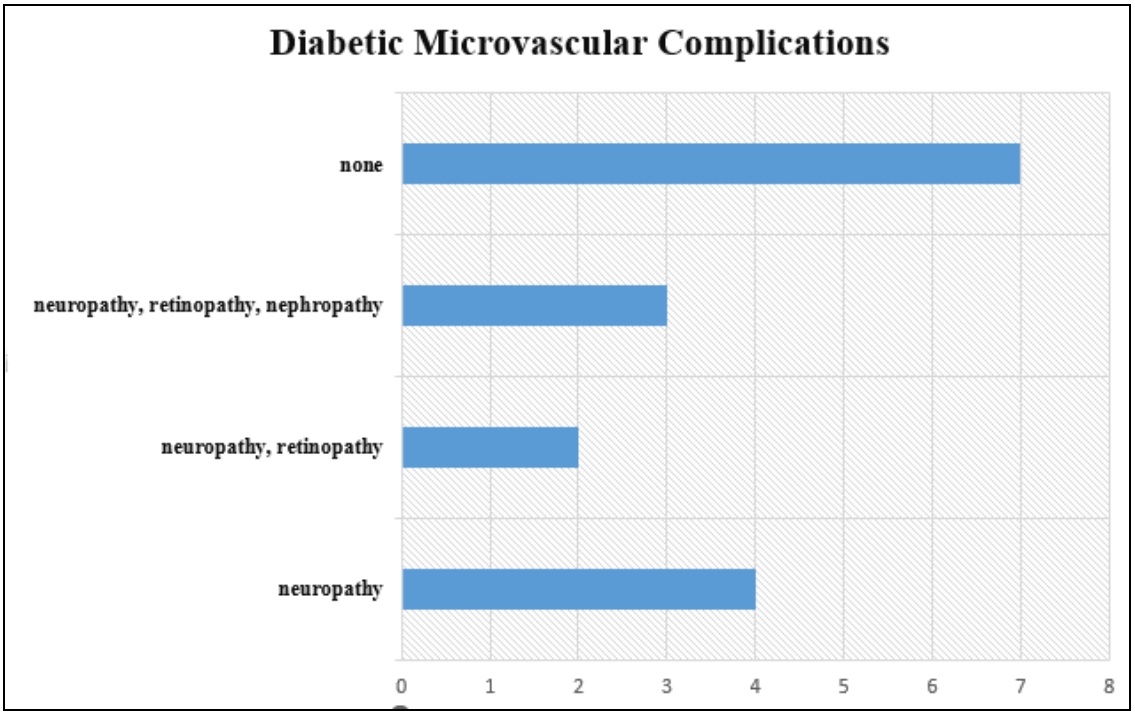


Figure 6.8. The occurrence of diabetic microvascular complications in T1DM.

- **<u>Correlations between the study variables:</u>**

A heatmap was generated to illustrate the relationships among the study variables. A heatmap is the visual representation of a correlation matrix which shows the correlation between each pair of variables in a dataset.

Figure 6.9. illustrates the heatmap, which provides visual insights into the strength and direction of the relationships between the variables.

As shown in the heatmap, the incidence of diabetic macrovascular complications is positively correlated with patient's age and the duration of diabetes disease (with percentages of 72%, 64% respectively). Another noteworthy correlation is that of the patient lipid profile and the occurrence of macrovascular events; as the correlation with Triglycerides and LDL are 79% and 23% respectively. And there is a strong negative correlation with HDL levels (-84%).

On the other hand, the incidence of diabetic microvascular complications is also positively correlated with patient's age and duration of diabetes but to a lesser extent than that of macrovascular complications (51% and 34% respectively). Furthermore, the relationship with the lipid profile is as follows, there is a positive correlation with triglycerides and LDL levels of 69% and 43%. And a negative correlation with HDL levels of -77%.

While the correlation between the incidence of both macrovascular and microvascular events at the same time is 78%.

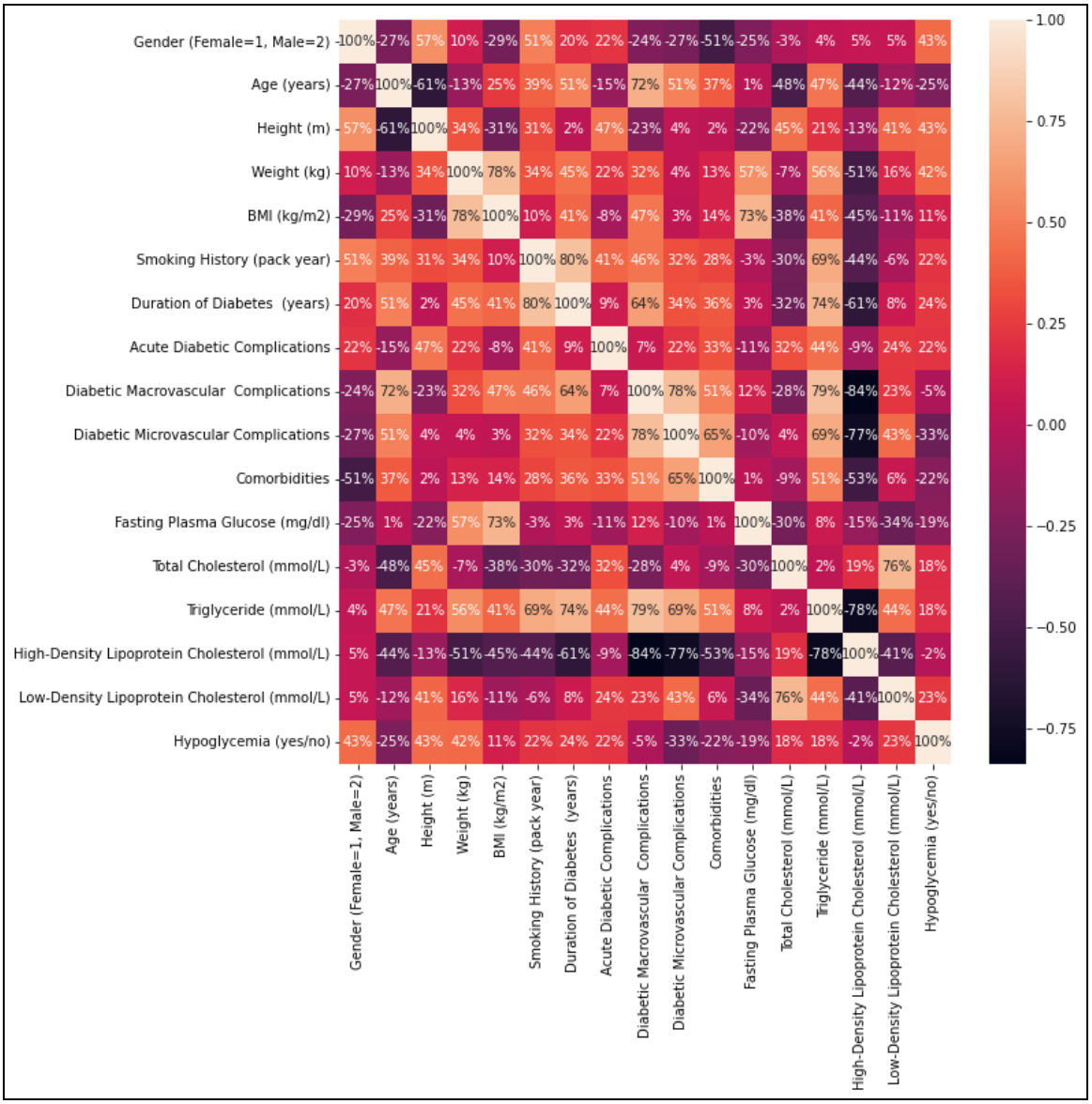


Figure 6.9. Heatmap of studied variables in T1DM data.

- **The characteristics of the T1DM CGM dataset:**

Hypoglycemia and hyperglycemia events are two potential risk factors for complications in diabetes. Hence, the time percentages of hypoglycemia (TBR) and hyperglycemia (TAR) events for each patient were calculated in Fig. 6.8. The horizontal axis represented each recording file of the patients with an order of TBR increasing, while the vertical axis represented the percentage of time (TAR, TIR and TBR) during the data collection period. The higher values of the TAR and TBR indicated that the patient's condition was more serious. To give a clearer view of the TBR, TIR and TAR in the dataset, we calculated the mean ± standard deviation of these values. For T1DM data, the mean ± standard deviation of the TIR were 54.7 ± 14.5% while the mean ± standard deviation of the TAR were 37.8 ± 18.8% and of the TBR were 7.5 ± 7%.

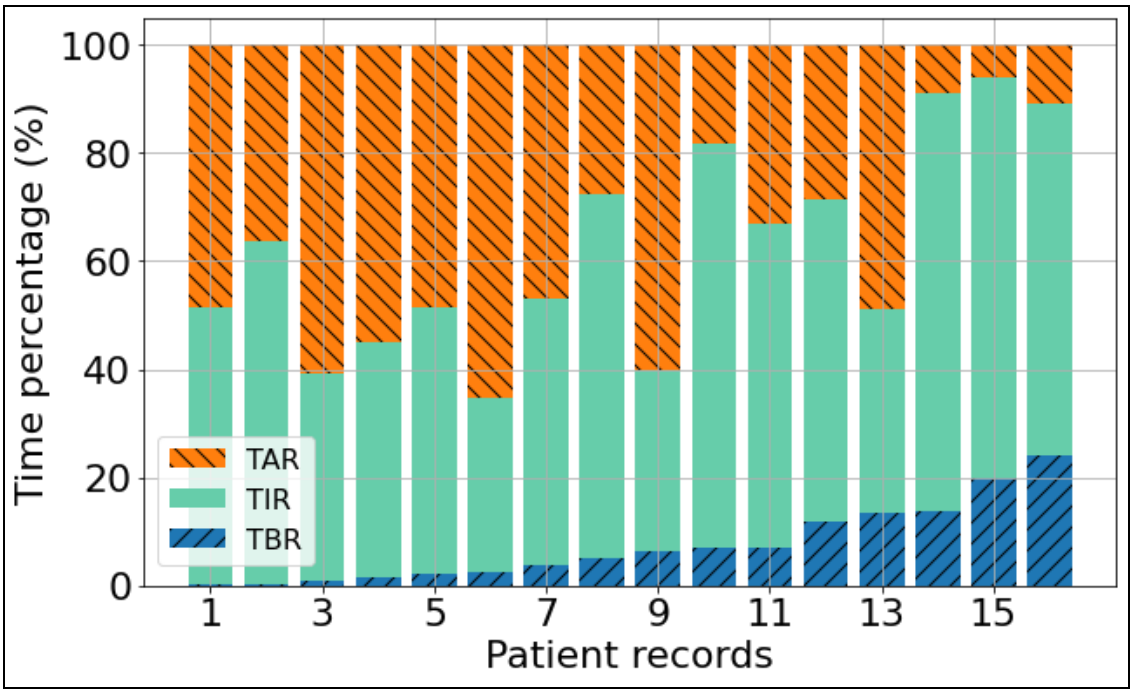


Figure 6.10. The average percentage of TBR (time below range), TIR (time in range) and TAR (time above range) for CGM in T1DM. TAR (37.8 ± 18.8%), TIR (54.7 ± 14.5%), TBR (7.5 ± 7.0%).

we also calculated the Auto-Correlation Coefficient (Acf) for three randomly selected patients in the T1DM dataset (1005_0_20210522, 1003_0_2021083, 1007_0_20210726). The autocorrelation function (ACF) measures the correlation between a time series and lagged versions of itself. It is commonly used to analyze the time series data to detect repeating patterns.

As shown in figure 6.12, The ACF plot for patient 1“1005_0_20210522” shows a strong positive correlation between the current value and the value 30 minutes ago. Also, there is a negative correlation between the current value and the value 20 minutes ago. This indicates that the time series tends to reverse its trend over short periods of time. And the pattern exhibits a gradual decay over time. The correlation coefficients remain above the significance threshold for several lags, indicating some degree of persistence in the data. This pattern suggests that the time series may be predictable to some extent, but the predictability decreases as we look further back in time.

The ACF plot for patient 2 “1003_0_20210831” shows a strong positive correlation between the current value and the value 30 minutes ago. But this pattern decays rapidly suggesting that there is little predictable pattern in the data. This patient may have highly variable glucose levels, with minimal persistence or predictability.

The ACF plot for patient 3 “1007_0_20210726” doesn’t show any significant correlations between the values. These random fluctuations around the zero line indicate weak or no autocorrelation in the time series data.

Overall, the ACF plots for these three patients suggest that their blood glucose levels are relatively predictable over time. This is likely due to the fact that they are all using continuous glucose monitors (CGMs) to track their blood glucose levels and are making adjustments to their insulin doses accordingly.

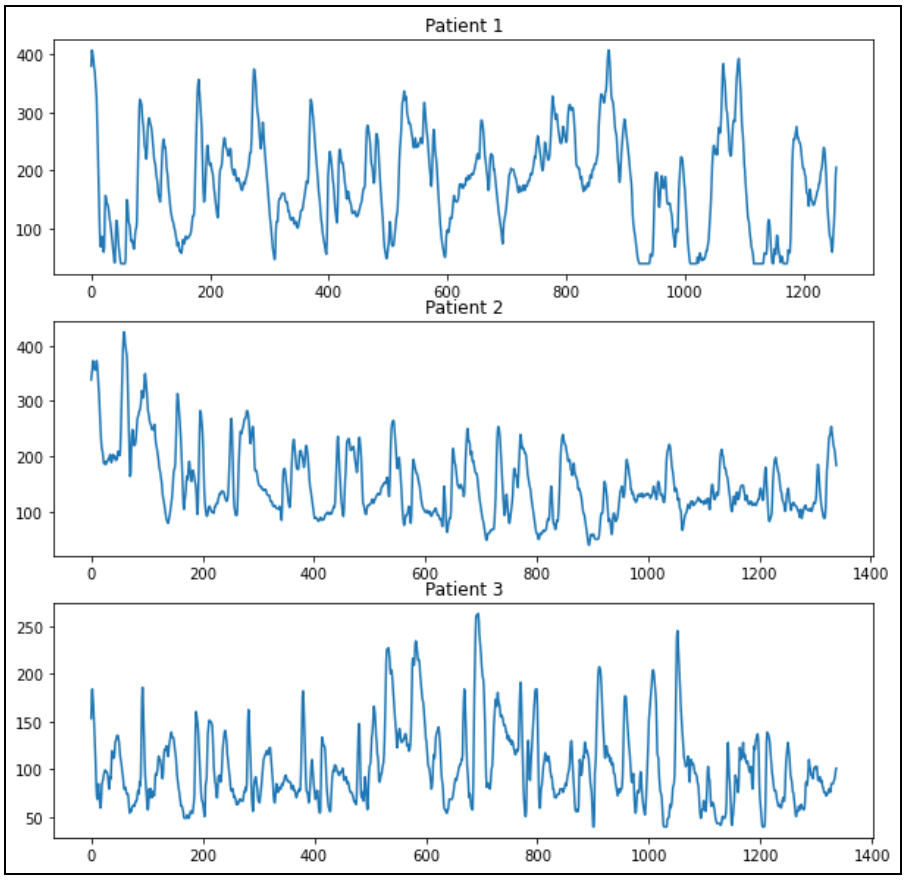


Figure 6.11. Randomly selected patients (1) 1005_0_20210522 and (2) 1003_0_20210831 and (3) 1007_0_20210726 in the ShanghaiT1DM for the distributions of glucose values of CGM readings.

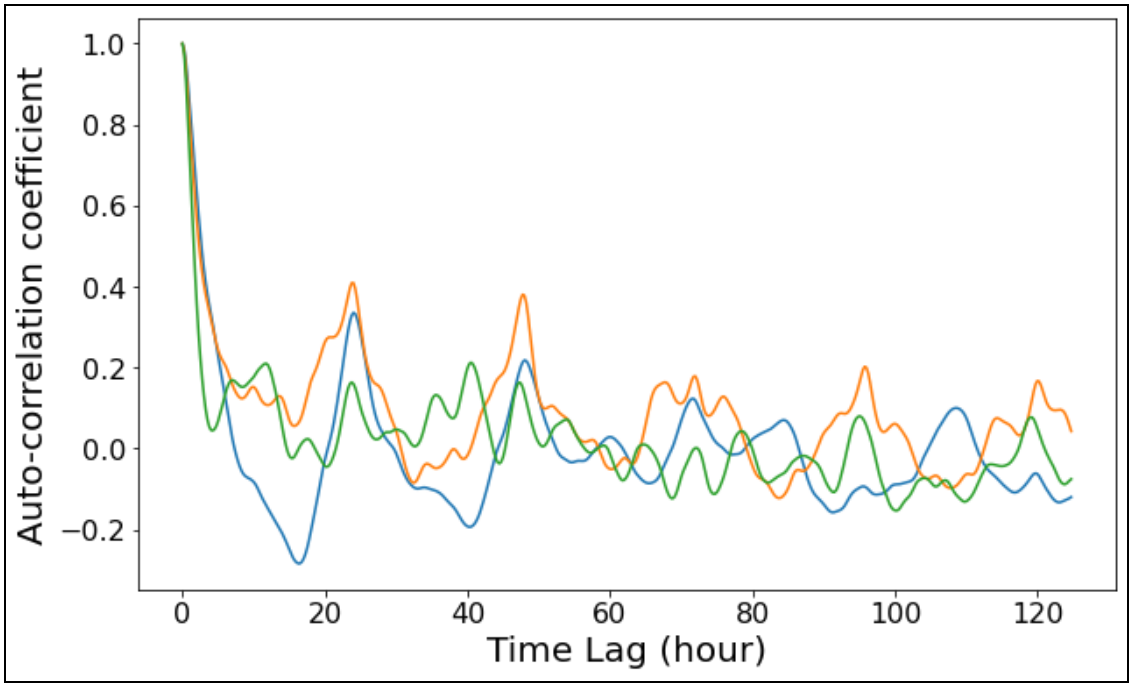


Figure 6.12. Auto-correlation coefficient of randomly picked three patients from the ShanghaiT1DM.

6.1.2. Type 2 Diabetes Mellitus data (T2DM):

- **Age:**

The average age of patients with T2DM in the data is 60.3 with a standard deviation of 14 as shown in table 6.5.

	N	Min	Max	Mean	Standard deviation
Age (years)	109	22	97	60.3	14

Table 6.5. Average age of T2DM patients.

and the age distribution of patients' age is shown in the figure 6.13.

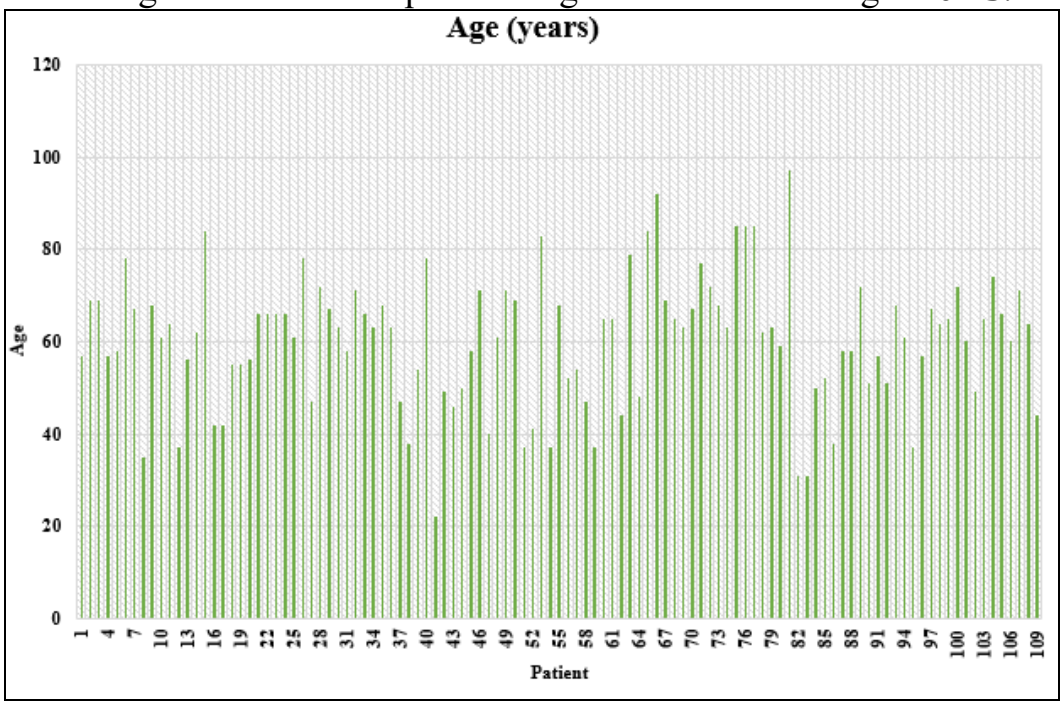


Figure 6.13. Age distribution in T2DM.

- **Fasting Plasma Glucose (mg/dl)**

In the data, the patient's fasting plasma glucose values range from 55.08 to 432 with a mean of 164.87 and a standard deviation of 62.75 as shown in table 6.6.

	N	Min	Max	Mean	Standard deviation
Fasting plasma glucose (mg/dl)	109	55.8	432	164.87	62.75

Table 6.6. statistics of patients' fasting plasma glucose in T2DM.

The following figure (6.14) shows the range of fasting plasma glucose among patients. which is an important metric in evaluating each patient's condition and glycemic control thus adjusting their treatment plan as necessary if the values are not satisfactory.

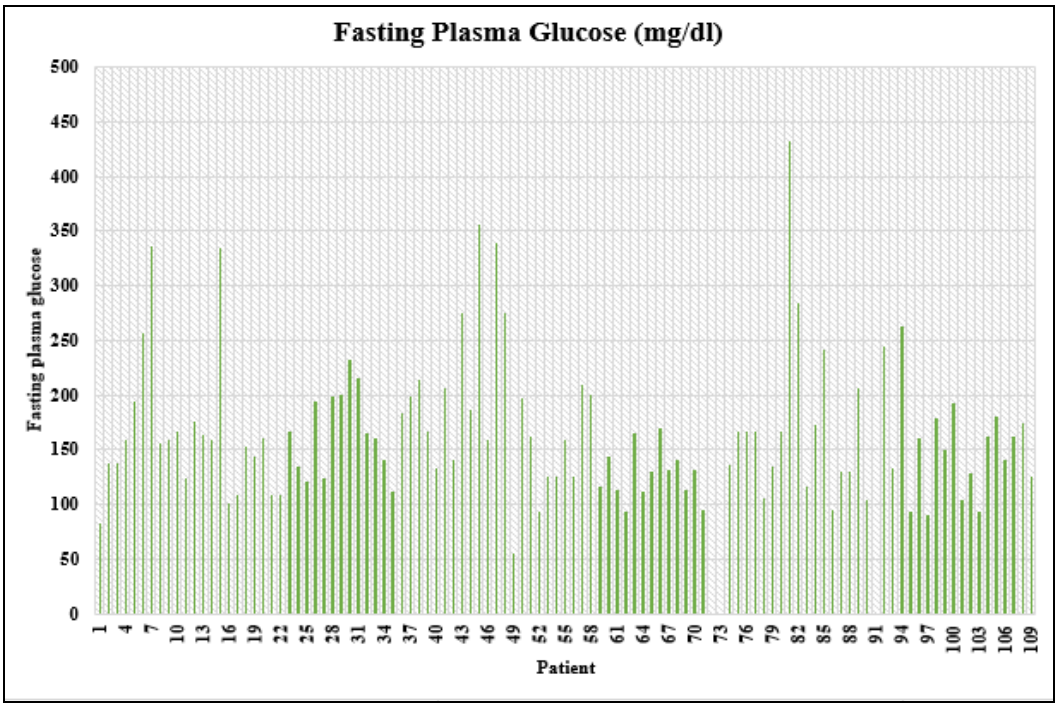


Figure 6.14. patients' fasting blood glucose in T2DM.

• 2hr Postprandial plasma glucose:

While fasting plasma glucose values are an important way to assess glycemic control. Physicians need to have an idea on the patient's glucose values after meals which provide an essential information on whether the patient is committed to the diabetes diet and their body's response to glucose load. As shown in table 6.7 and figure 6.15, patients' 2 hr. postprandial glucose values range from 72.54 to 372.96 with a mean of 268.76 which gives an understanding that most of the patients in this study have poor glycemic control since as physicians we aim for a postprandial glucose value less than 180 mg/dl.

	N	Min	Max	Mean	Standard deviation
2hr postprandial plasma glucose (mg/dl)	109	97.08	610.38	264.76	96.04

Table 6.7. Statistics of T2DM patients' 2-hr postprandial plasma glucose.

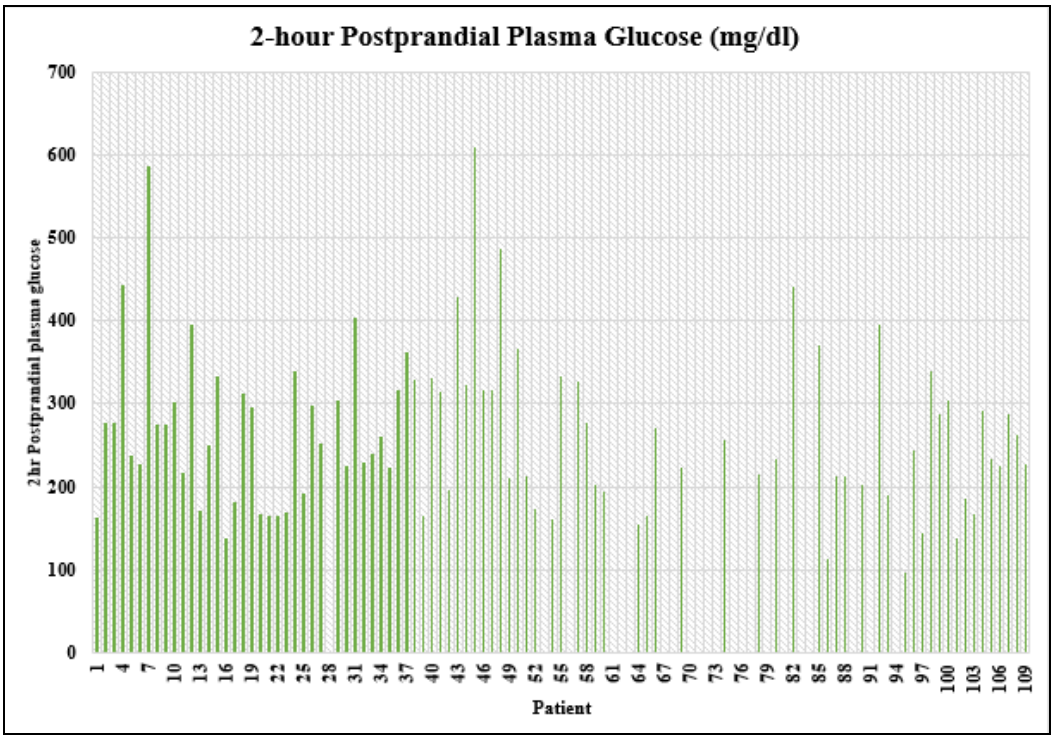


Figure 6.15. T2DM patients' 2-hr postprandial plasma glucose.

- **HbA1c:**

HbA1c is an important metric to evaluate the diabetic patient. It represents the patient's glycemic control over the previous 3 months period and it offers an immense help in deciding to adjust the treatment plan. in the available data the patients' HbA1c ranges from 23.49 to 144.82 as shown in table 6.8 and figure 6.16. in treatment goals the preferable value of HbA1c is less than 53 mmol/mol.

	N	Min	Max	Mean	Standard deviation
HbA1c (mmol/mol)	109	23.49	144.82	74.65	26.57

Table 6.8. HbA1c descriptive statistics in T2DM.

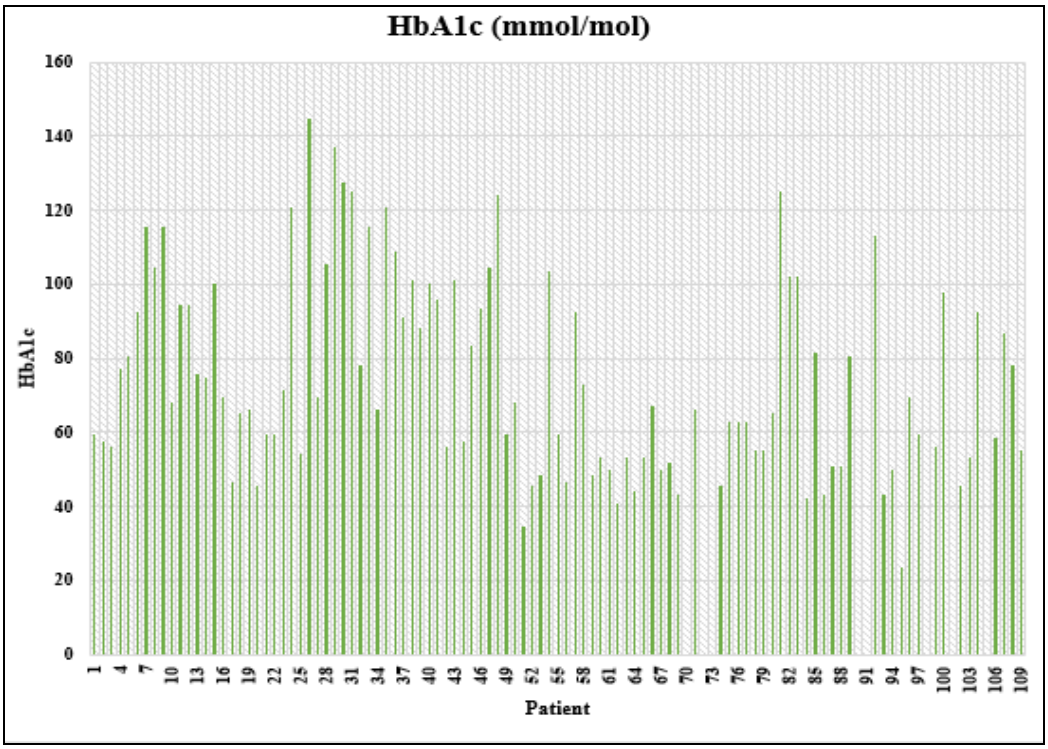


Figure 6.16. distribution of HbA1c in T2DM patients.

- **Acute Complications; Diabetic ketoacidosis and hypoglycemia**

The most important goal of treatment is to avoid acute complications of diabetes. These complications can have catastrophic effects of patient and may even lead to death in severe cases.

The two main acute complications are diabetic ketoacidosis and hypoglycemia.

Diabetic Ketoacidosis: is an emergency that occurs mainly in T1DM patients. and is the result of extremely elevated glucose values. And while it can occur in T2DM none of the study patient experienced DKA in the duration of the study.

Hypoglycemia: another acute complication of diabetes treatment and it's the results of low glucose values. All diabetic patient on insulin or other glucose lowering drugs are susceptible to hypoglycemia episodes. These episodes could be an important indicator to reassess the treatment and adjust as necessary. As shown in figure 6.17. out of the 109 patients in the dataset, only 10 had hypoglycemic episodes while the other 99 didn't experience hypoglycemic episodes in the duration of the study.

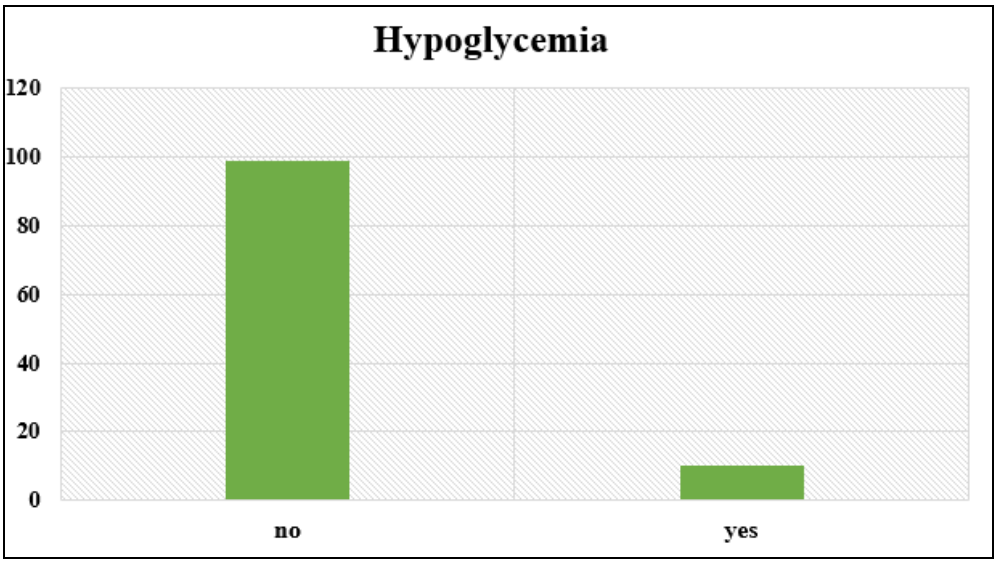


Figure 6.17. the incidence of hypoglycemic episode in T2DM patients.

• Diabetic Macrovascular Complications:

over the years, diabetic patients are susceptible to the chronic diabetic complications especially the ones with poor glycemic control. As shown in figure 6.18, The patients were assessed for macrovascular complications of diabetes which include; peripheral arterial disease, coronary heart disease and cerebrovascular disease.

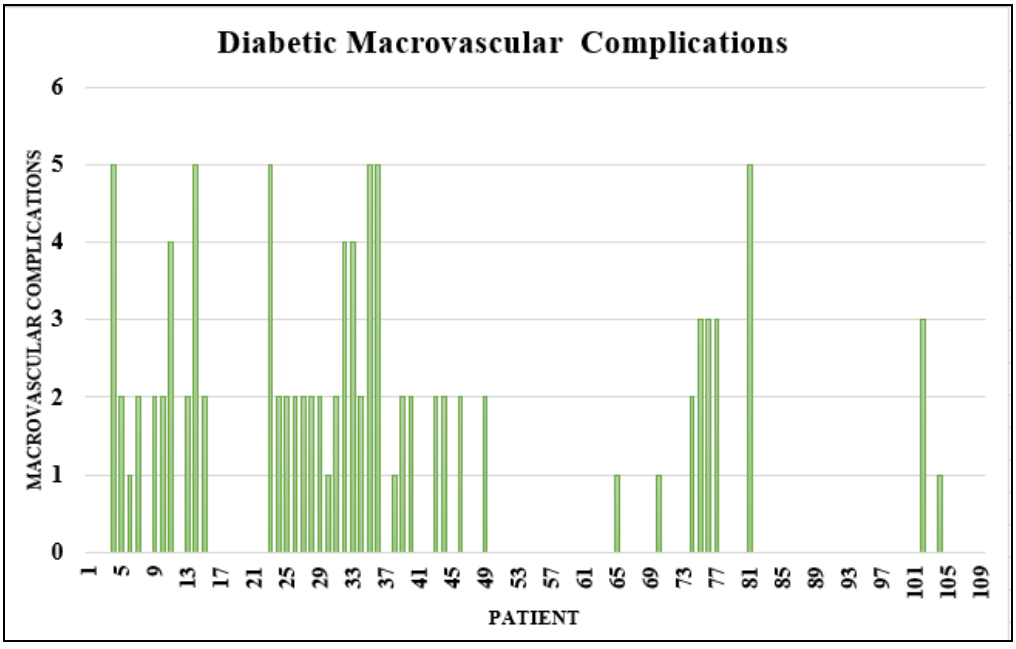


Figure 6.18. The occurrence of diabetic macrovascular complications in T2DM (0: none, 1: coronary heart disease, 2: peripheral arterial disease, cerebrovascular disease, 4: peripheral arterial disease, cerebrovascular disease, 5: peripheral arterial disease, coronary heart disease).

• Diabetic Microvascular Complications:

The microvascular complications of diabetes include; Neuropathy, Nephropathy and Retinopathy. the following figure 6.19. shows the occurrence of these complications in T2DM data.

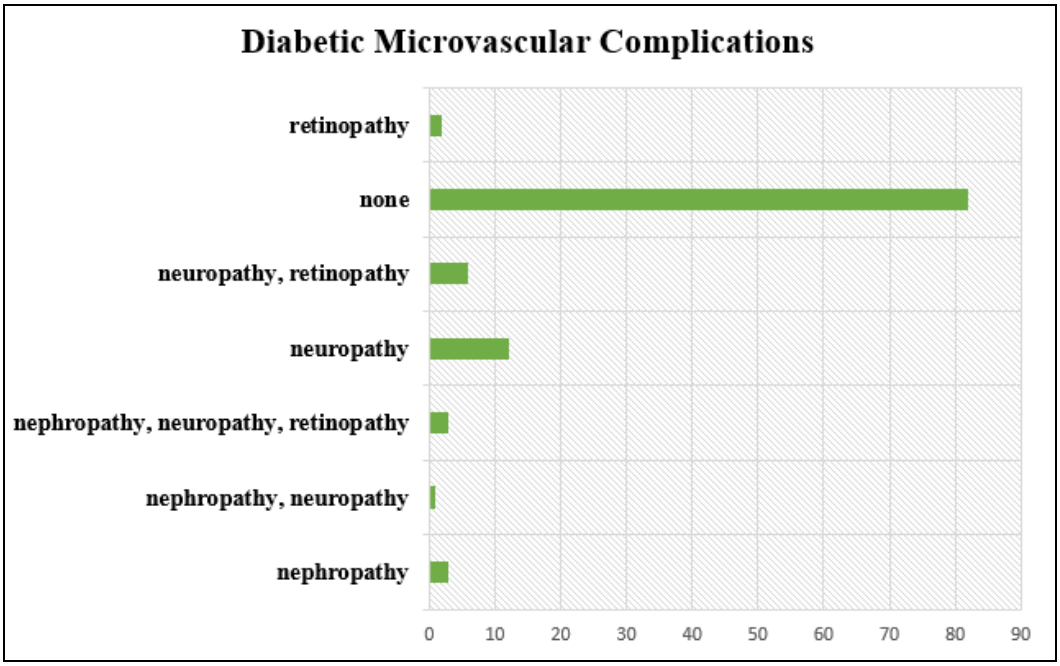


Figure 6.19. The occurrence of diabetic microvascular complications in T2DM.

➢ Correlations between the study variables:

A heatmap was generated to illustrate the relationships among the study variables. A heatmap is the visual representation of a correlation matrix which shows the correlation between each pair of variables in a dataset.

Figure 6.20. illustrates the heatmap, which provides visual insights into the strength and direction of the relationships between the variables.

While the incidence of diabetic macrovascular complications is correlated with patient's age and the duration of diabetes disease (with percentages of 32%, 27% respectively). it is less than the T1DM high correlation percentages.

On the other hand, the incidence of diabetic microvascular complications is also correlated with patient's age and duration of diabetes (9% and 33% respectively). It's also to a lower extent than T1DM.

While the correlation between the incidence of both macrovascular and microvascular events at the same time is 64%.

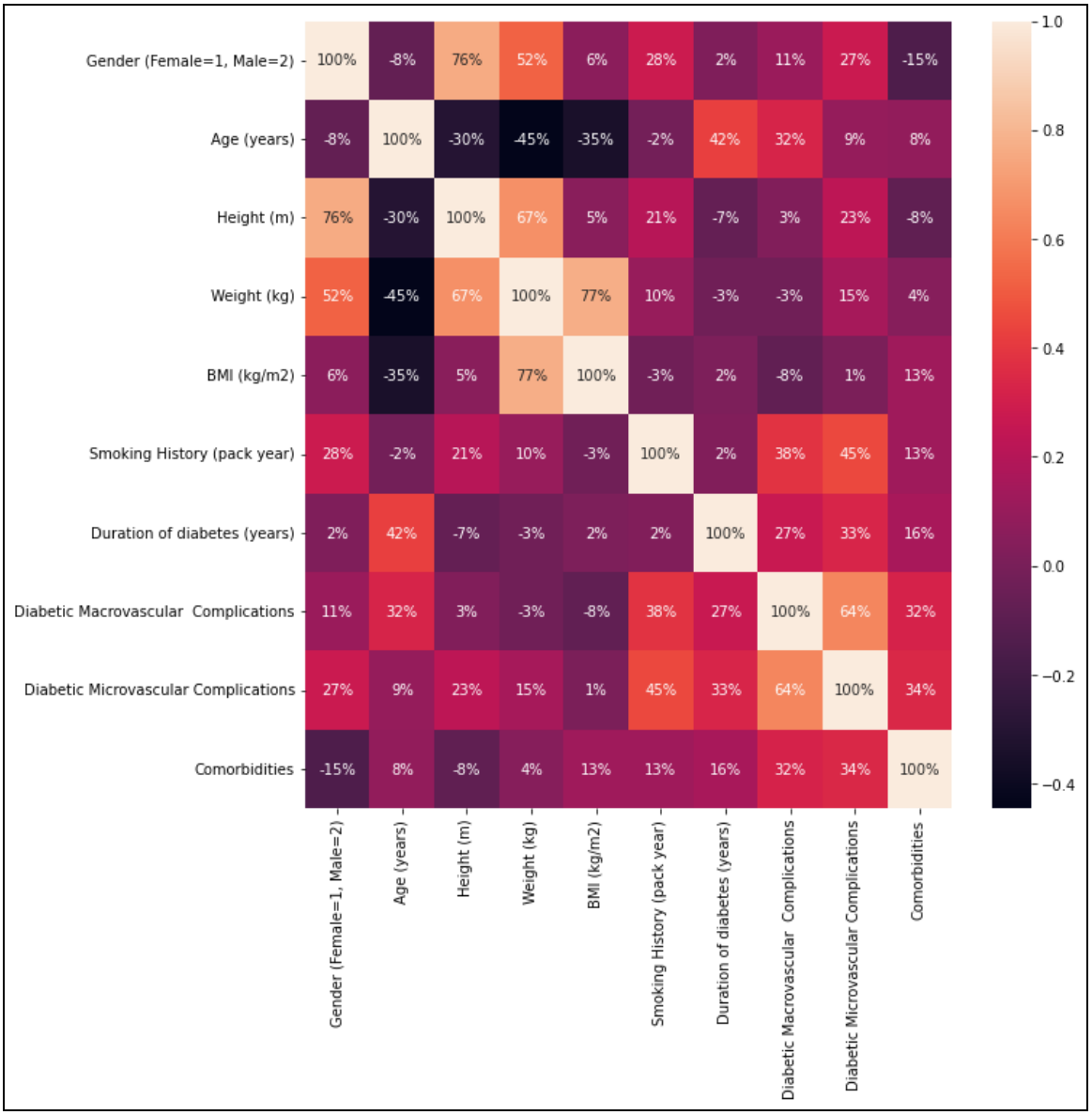


Figure 6.20. Heatmap of studied variables in T2DM data.

➢ The characteristics of the T2DM CGM dataset:

Hypoglycemia and hyperglycemia events are two potential risk factors for complications in diabetes. Hence, the time percentages of hypoglycemia (TBR) and hyperglycemia (TAR) events for each patient were calculated in Fig. 6.21. The horizontal axis represented each recording file of the patients with an order of TBR increasing, while the vertical axis represented the percentage of time (TAR, TIR and TBR)

during the data collection period. The higher values of the TAR and TBR indicated that the patient's condition was more serious. To give a clearer view of the TBR, TIR and TAR in the dataset, we calculated the mean ± standard deviation of these values. For T2DM data, the mean ± standard deviation of the TIR were 77.7 ± 18.1% while the mean ± standard deviation of the TAR were 20± 18.4% and of the TBR were 2.4 ± 7.2%.

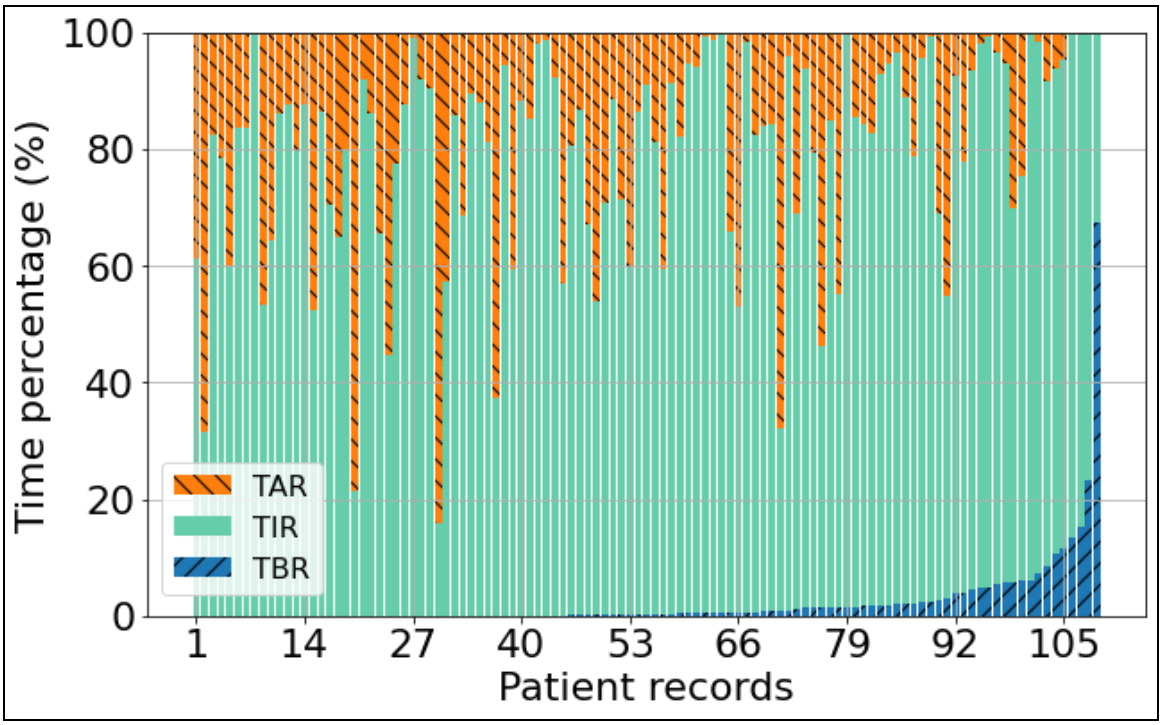


Figure 6.21. The average percentage of TBR (time below range), TIR (time in range) and TAR (time above range) for CGM in T2DM. TAR (20.0 ± 18.4%), TIR (77.7 ± 18.1%), TBR (2.4 ± 7.2%).

we also calculated the Auto-Correlation Coefficient (Acf) for three randomly selected patients in the T2DM dataset (2016_0_20201224, 2017_0_20210102, 2018_0_20210420). The autocorrelation function (ACF) measures the correlation between a time series and lagged versions of itself. It is commonly used to analyze the time series data to detect repeating patterns.

As shown in figure 6.23, The ACF plot for patient 1"2016_0_20201224" shows a strong positive correlation between the current value and the value 30 minutes ago, indicating that the time series tends to follow a consistent pattern over time. This means that if the value 30 minutes ago was high, the current value is also likely to be high, and vice versa. On the other hand, the ACF shows a negative correlation with the value 15

minutes ago. This indicates that the time series tends to reverse its trend over short periods of time. In other words, if the value 15 minutes ago was high, the current value is likely to be low, and vice versa. These observations suggest that the time series is mean-reverting, meaning that it tends to return to its average value over time.

The ACF plot for patient 2 “2017_0_20210102” shows a strong positive correlation between the current value and the value 25 minutes ago. a negative correlation with the value 40 minutes ago indicating that the data is mean-reverting.

The ACF plot for patient 3 “2018_0_20210420” shows a strong positive correlation between the current value and the value 30 minutes ago. Additionally, there is a lower positive correlation between the current value and the value 15 minutes ago. This suggests that the time series tends to maintain its direction over short periods of time, but the strength of this tendency is weaker compared to the 30-minute correlation. Based on these observations, we can infer that the time series exhibits a persistent pattern, where the current value is influenced by the values from the recent past. This pattern suggests that the time series may be predictable to some extent, and future values may be forecasted based on historical data.

Overall, the ACF plots for these three patients suggest that their blood glucose levels are relatively stable and do not fluctuate much over time. This is likely due to the fact that they are all using continuous glucose monitors (CGMs) to track their blood glucose levels and are making adjustments to their insulin doses accordingly.

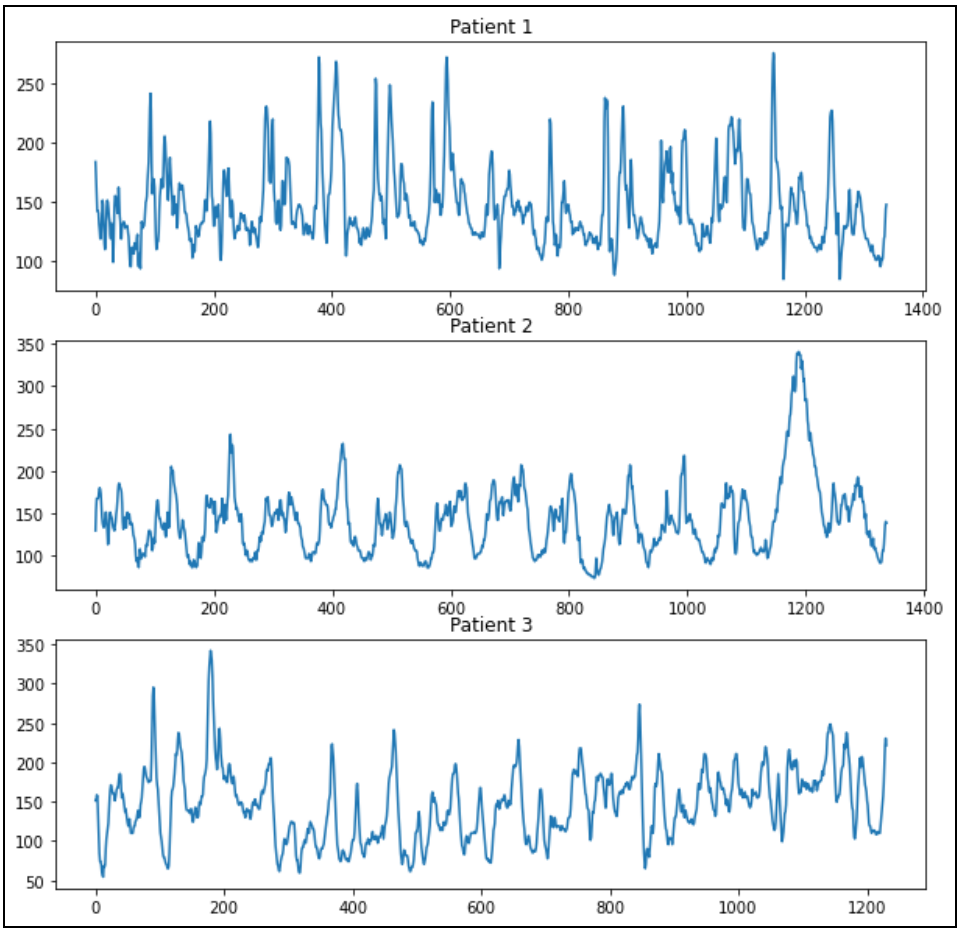


Figure 6.22. Randomly selected patients (1) 2016_0_20201224 and (2) 2017_0_20210102 and (3) 2018_0_20210420 in the ShanghaiT2DM for the distributions of glucose values of CGM readings.

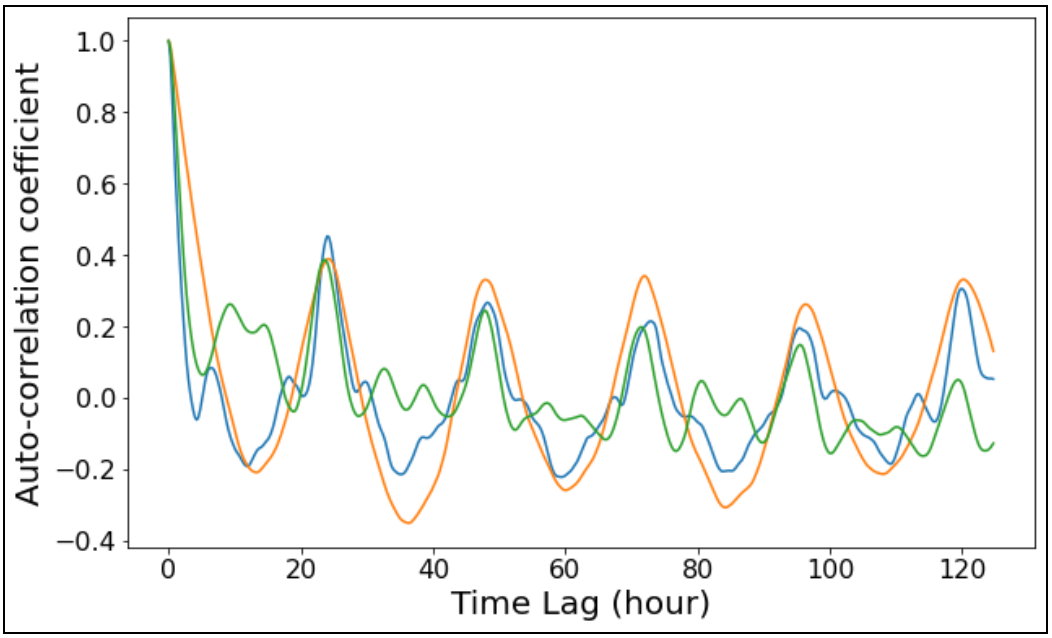


Figure 6.23. Auto-correlation coefficient of randomly picked three patients from the ShanghaiT2DM.

6.2. Neural Network Model (LSTM)

6.2.1. Type 1 Diabetes Mellitus data (T1DM):

The Data was divided into a training set comprising 70% of the total data, and a test set comprising 20% of the total data and a validation set comprising the remaining 10% of the total data.

we applied the LSTM model shown in figure 5.1. and figure 5.2, on the patient "1002_0_20210504" and calculated the RMSE value to assess the performance of the selected model.

Root Mean Square Error: To compute the RMSE [52], we first take the square of the difference between the actual and predicted values of every record. We then take the average value of these squared errors and calculate the root of this value. If the predicted value of the i^{th} record is P_i and the actual value is A_i, then the RMSE is:

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n}(P_i - A_i)^2}{n}}$$

in the proposed model, we achieved an RMSE of (9.78 mg/dl) in the T1DM dataset. the following figure (6.24), illustrates the difference between the actual and the values predicted using the LSTM model.

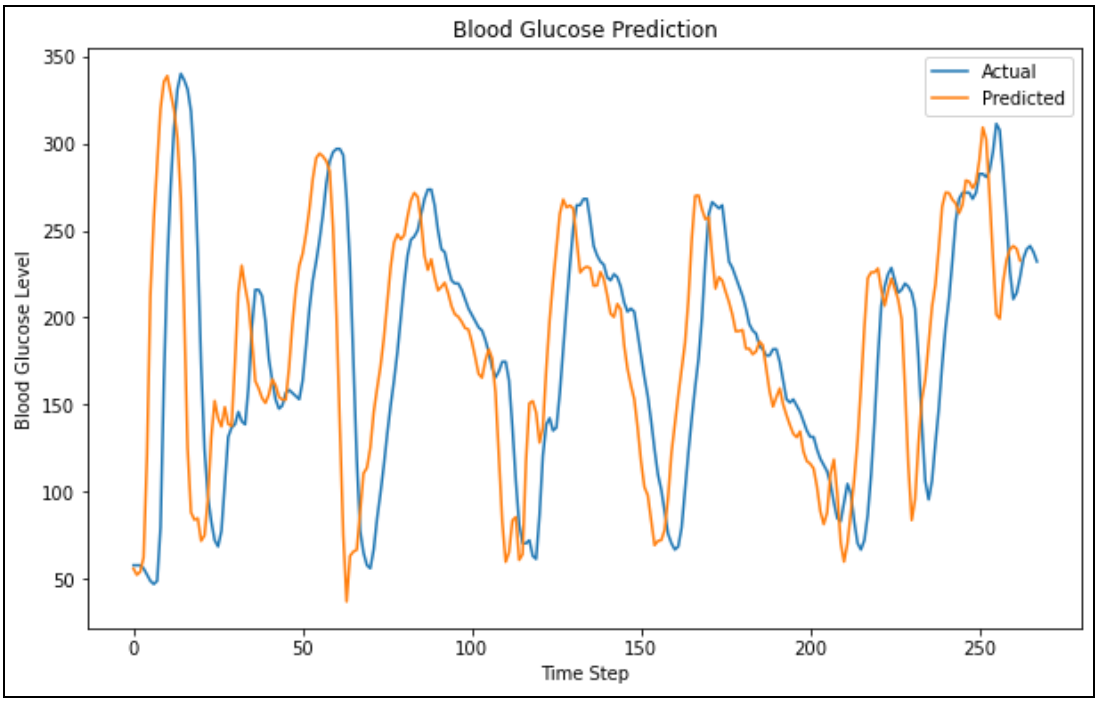


Figure 6.24. Results of LSTM model application on T1DM data.

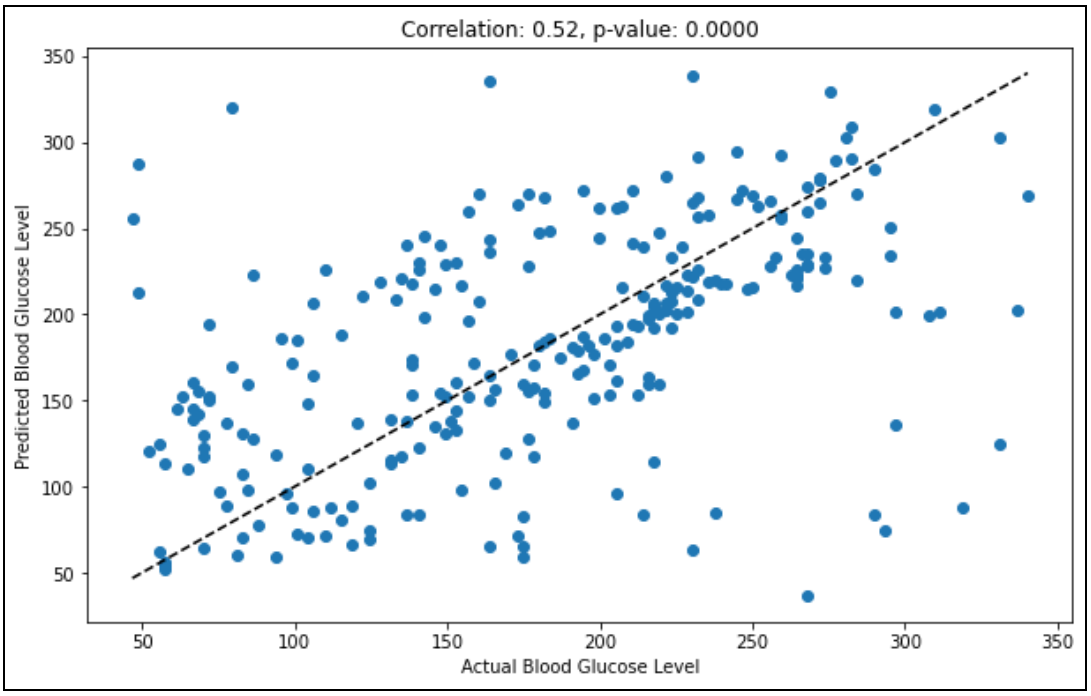


Figure 6.25. scatterplot of the actual and predicted values in T1DM data and the calculated correlation between them (correlation: 0.52).

Furthermore, we plotted the results on a Clarke Error Grid to validate the model outcome (figure 6.26). A Clarke Grid Analysis was developed in

1987 and is used to evaluate the clinical significance of inaccuracies in the measurements of blood glucose concentration.

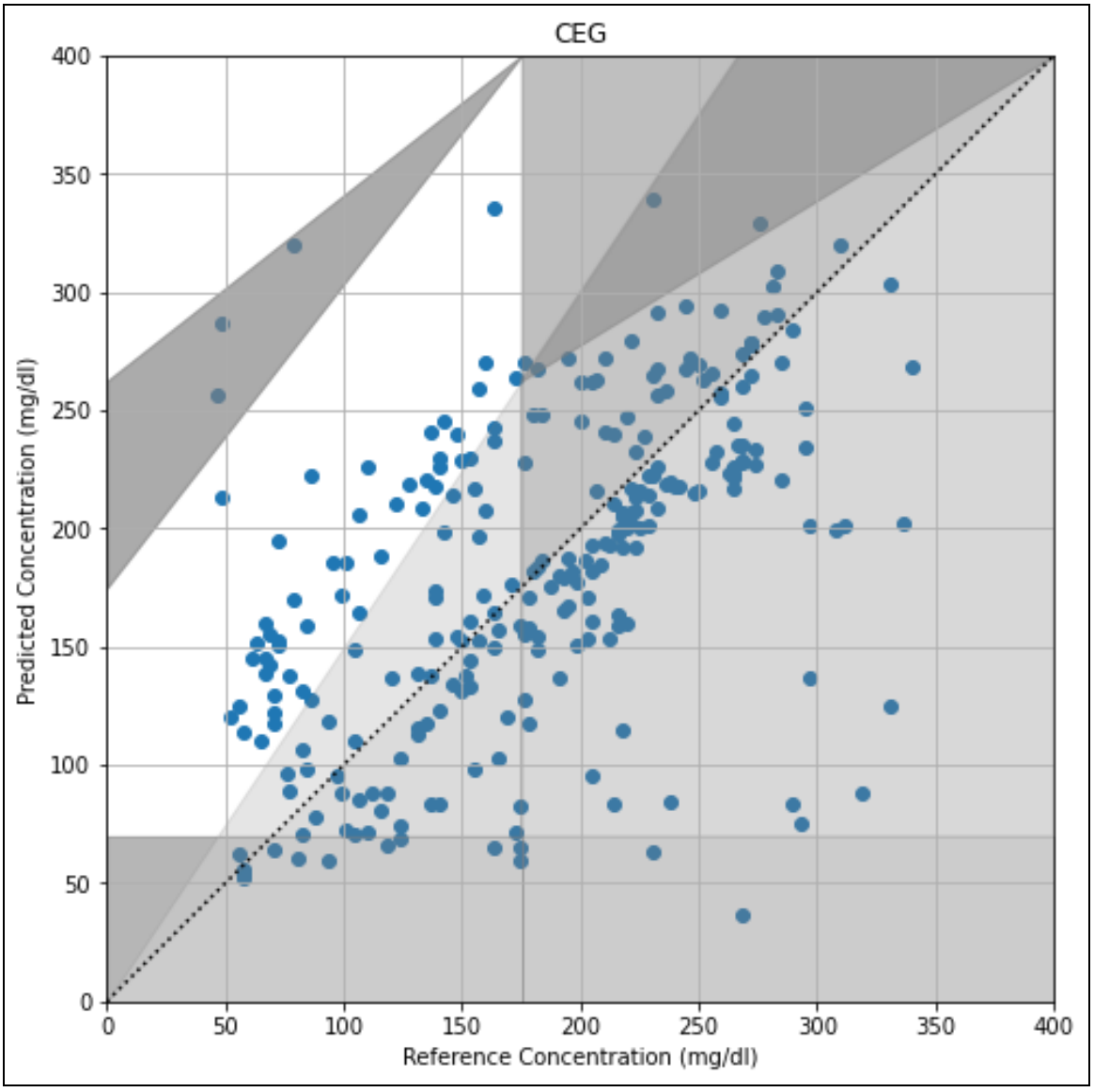


Figure 6.26. Clarke error grid evaluation of glucose prediction safety in T1DM dataset.

6.2.2. Type 2 Diabetes Mellitus data (T2DM):

The Data was divided into a training set comprising 70% of the total data, and a test set comprising 20% of the total data and a validation set comprising the remaining 10% of the total data.

we applied the LSTM model shown in figure 5.1. and figure 5.2, on the patient “2001_0_20201102” and calculated the RMSE value to assess the performance of the selected model.

in the proposed model, we achieved an RMSE of (4.40 mg/dl) in the T2DM dataset. the following figure (6.27), illustrates the difference between the actual and the values predicted using the LSTM model.

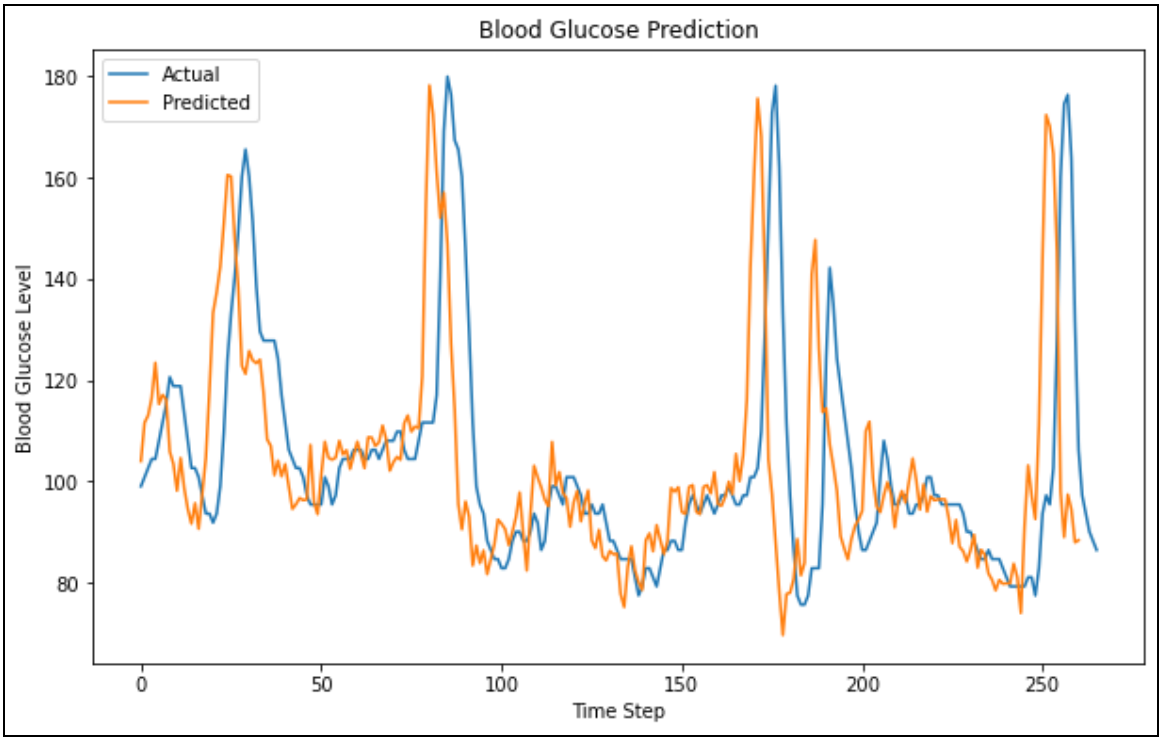


Figure 6.27. Results of LSTM model application on T2DM data.

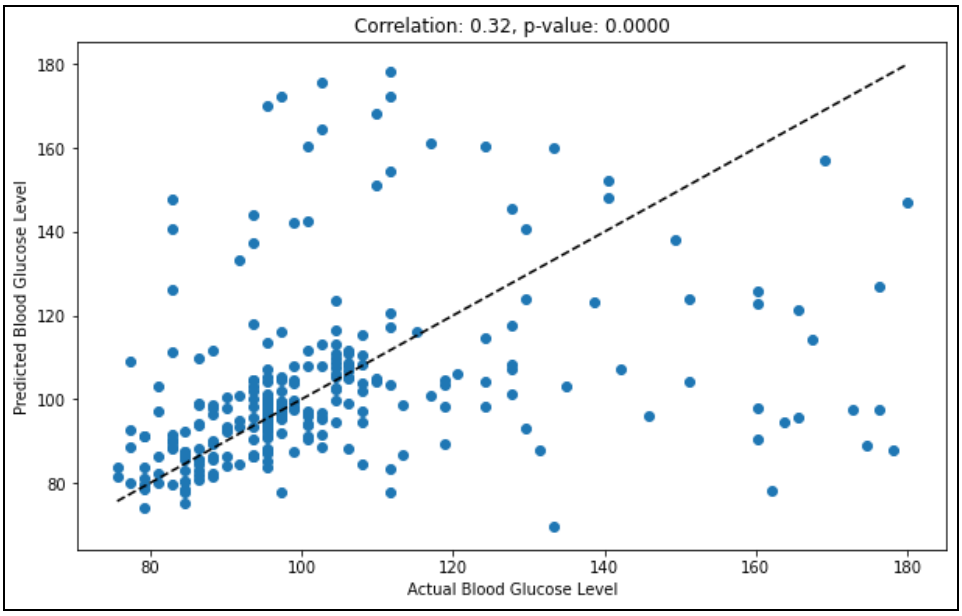


Figure 6.28. scatterplot of the actual and predicted values in T2DM data and the calculated correlation between them (correlation: 0.32).

Furthermore, we plotted the results on a Clarke Error Grid to validate the model outcome (figure 6.29) and assess the clinical significance of our results.

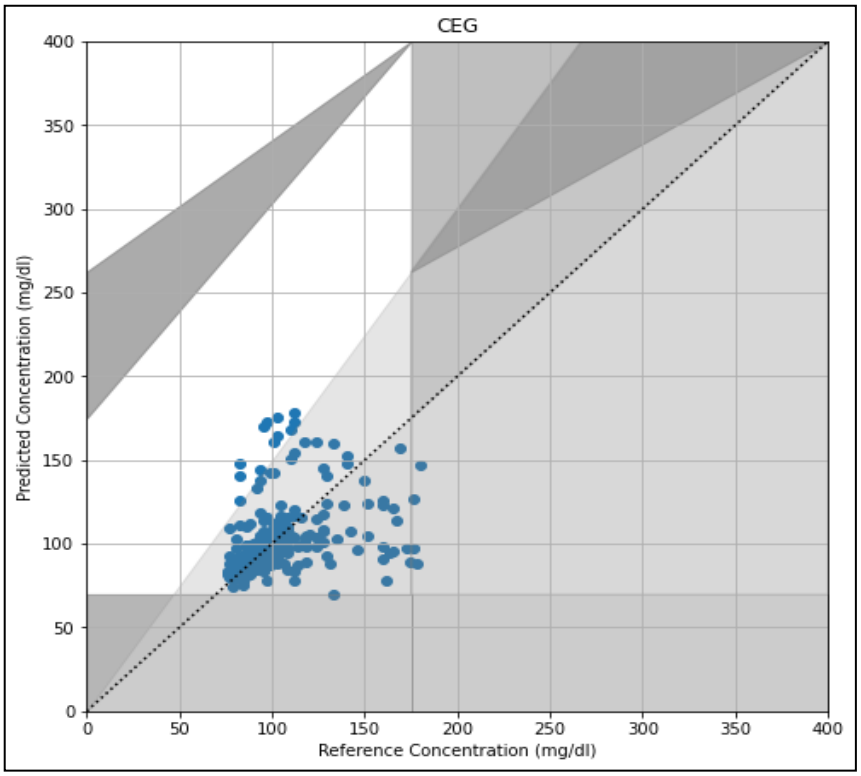


Figure 6.29. Clarke error grid evaluation of glucose prediction safety in T2DM dataset.

6.3. Discussion

One of the most important goals in diabetes treatment is avoiding fluctuations in glycemia in diabetic patients. Experiencing excessive hypo/hyperglycemia episodes could lead to devastating complications and low life quality for DM patients. Physicians rely on different glucose monitoring devices to monitor patients and adjust the treatment plan as efficiently as possible.

The use of CGM devices gives physicians plenty of information on the patient's glycemic control at home. But the enormous amount of data that can't always be interpreted manually could prevent the optimal benefit of CGM. Thus, the use of machine learning and deep learning techniques could open opportunities to better analyze CGM data and discover existence of trends. By understanding the glycemic patterns of each patient, we could achieve a more personalized approach to treatment.

In this study, we used a RNN model comprising of two layers an LSTM layer and a dense layer, as well as employing a ReLU activation function and RMSE loss function. We applied the proposed model on both T1DM and T2DM datasets and assessed the performance of the model with the RMSE metric. We achieved a result of (RMSE: 9.78 mg/dl) for the LSTM model in T1DM patients' data and (RMSE: 4.40 mg/dl) in T2DM patients' data. Overall, our models demonstrated high prediction accuracy, supported by low RMSE values. But the model performed better in T2DM with a lower RMSE than that of T1DM.

Several studies were conducted in order to utilize the enormous data supplied by CGM sensors, for the purpose of improving DM patients' glycemic control and quality of life. One such study by Eleonora Maria Aiello et al. [33] used Deep Glucose Forecasting that employed two-headed LSTM network and achieved a RMSE of (27.29 mg/dl) that drops to (21.09 mg/dl) after further tuning. Different research by Yixiang Deng et al [34] utilizes CNN, RNN (LSTM), a mixup and time series generative adversarial networks (TimeGAN) and proposed their best performing model (CNN+Transfer2) with an accuracy of 95.98%, sensitivity of 59.9% and a specificity of 98.15%. Another very important model was used by J. Quetzalcòatl Toledo Marín et al [31]. This model employed the same BG risk score formula used in our study that was

originally proposed by Kovatchev. This study trained several models including; CNN, GRU, RNN and a LSTM network with a resulting RMSE of (16 mg/dl, 24 mg/dl, 37 mg/dl) for CNN prediction horizon of 15, 30, and 60 minutes respectively.

Most importantly, the ability to apply this model in real life setting is the main goal of using deep learning models. thus, we assessed the clinical safety of glucose prediction using the Clarke Error Grid (CEG). In T1DM data, most of the predictions fell in zones A or B which are either accurate of clinically benign with very few predictions were inaccurate or could be clinically harmful. Alternatively, in T2DM data most of the predictions were in zone A which is clinically accurate while the rest of the predictions were in Zone B which is clinically benign. In comparison to the aforementioned studies, our results (RMSE: 9.78 mg/dl in T1DM dataset and RMSE:4.40 mg/dl in T2DM dataset) are noteworthy and support further experimentation in the use of LSTM networks in future research and hopefully implementing deep learning further in the clinical decision making and improving healthcare on a broader scale.

6.4. Conclusion

In this study, we show that our LSTM model was able to accurately and safely predict glucose values. In addition, translation of our prediction models to individuals with both type 1 diabetes showed encouraging results. We observed high precision in predictions. As such, the prediction model can be used to improve closed-loop insulin delivery systems by overcoming sensor delay. In addition, longer prediction intervals may be used to safely bridge periods of sensor malfunction. On another note, analyzing CGM data in T2DM and accurately predicting patient's glucose at different intervals offers an immense help in improving the drug choices based on the trends in the data.

Future research should validate our findings by replicating the results in a larger sample of individuals with both type 1 and type 2 diabetes. Another area that could be explored in the future is the inclusion of meals and insulin doses delivered to the patient in the model in order to computationally decide the optimal dose of insulin needed independent of patient's input.

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